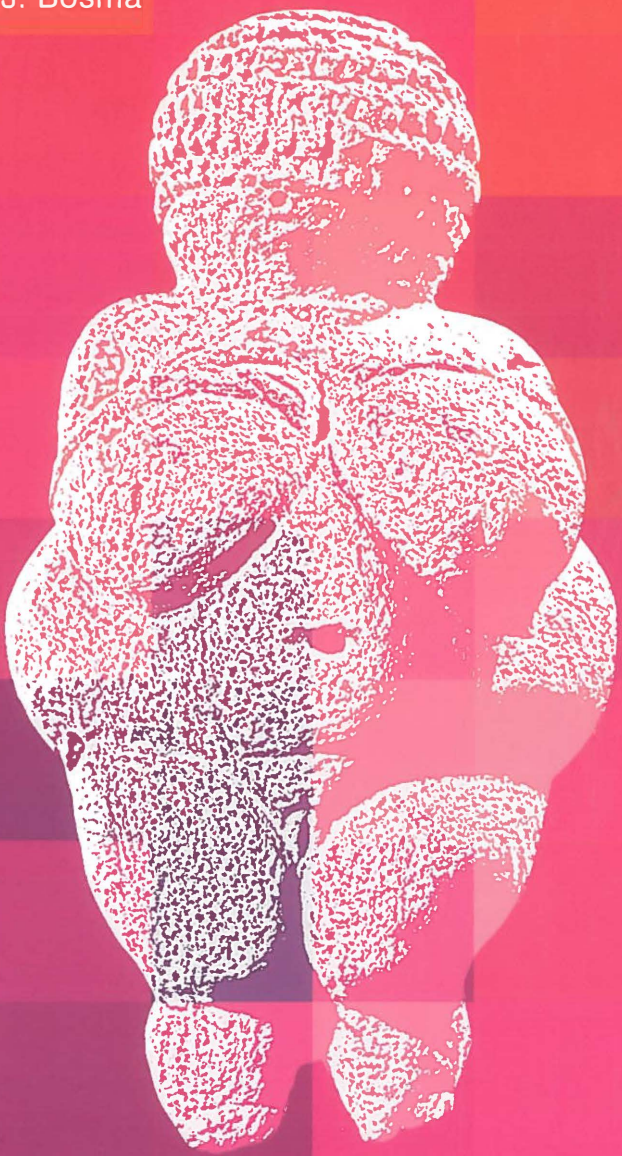
Role of renal hemodynamics in obesity associated renal risk

Renate J. Bosma



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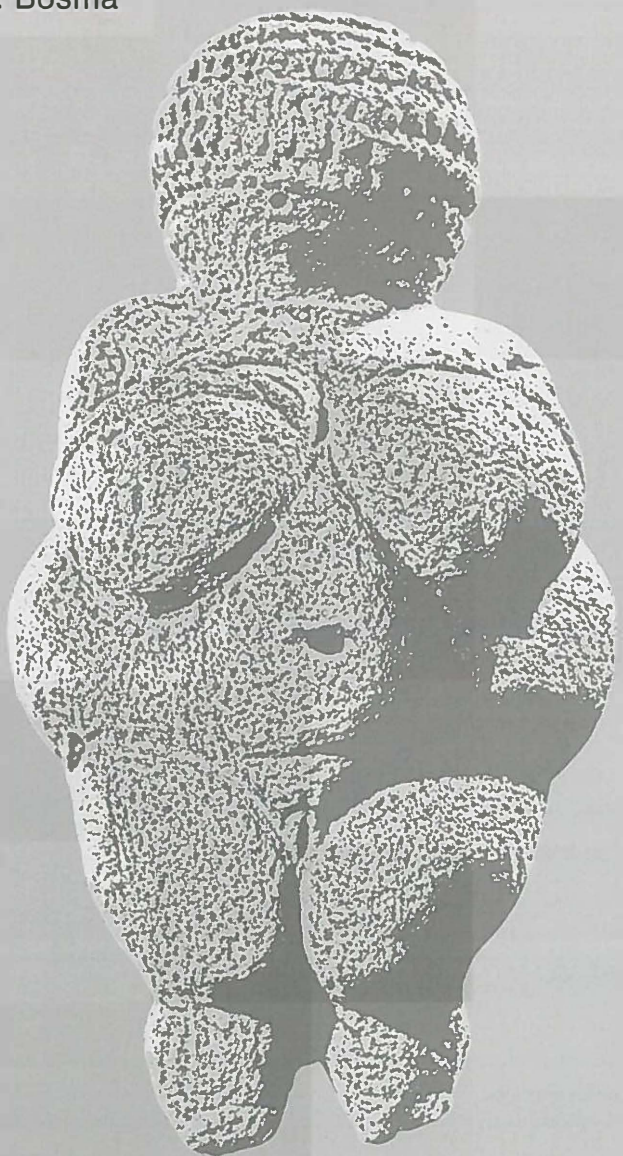

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Paranimfen

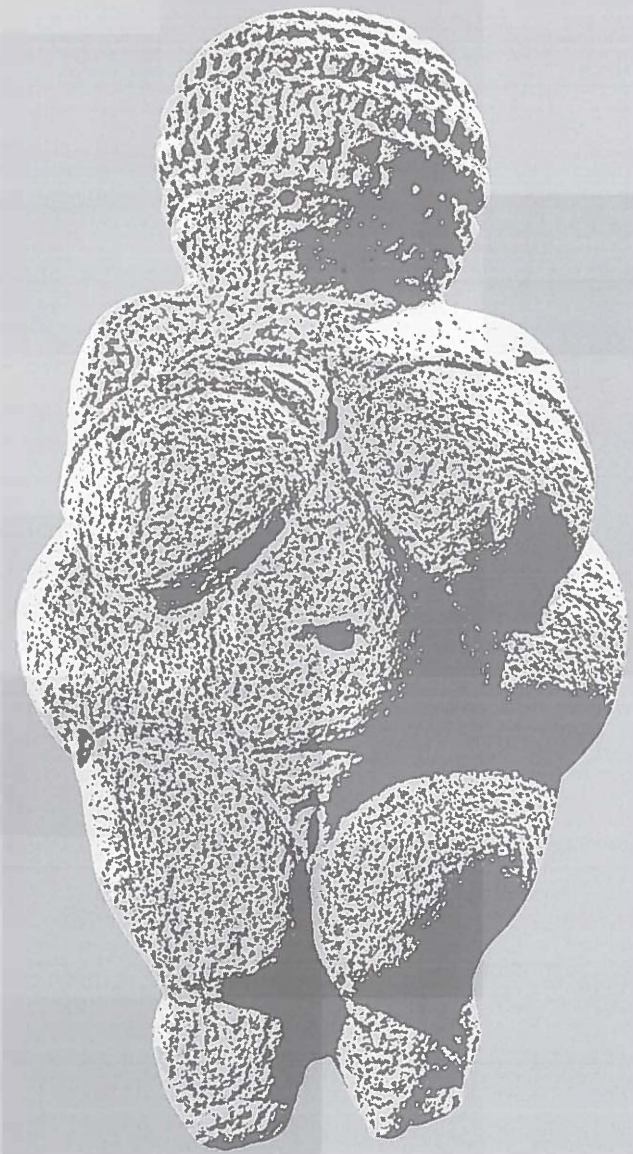
Jos Berends

Niels Bosma

"*The kidney is so important that, in contrast to the heart and the brain, the body has two instead of one*"

Anonymous nephrologist

Contents



Chapter 1

Introduction

Background

The epidemic of obesity

Hippocrates wrote: "Corpulence is not only a disease itself, but the harbinger of others", recognizing that obesity is a medical condition that also leads to many comorbidities (1). Whereas, apparently, obesity was recognized as a morbid condition in ancient times, it may well turn out to be the major health problem of the 21st century, due to its increasing prevalence and the associated morbity and mortality. Obesity is associated with an increased mortality in selected populations – with studies reporting a 30-70% increased risk of death among subjects with a body mass index (BMI) of 30 kg/m² or higher (2-4), mainly due to an elevated cardiovascular risk. Several cardiovascular risk factors are promoted by obesity. First, it is a main factor in the increasing incidence of insulin resistance, and eventually type 2 diabetes mellitus. Furthermore, it exerts adverse influences on blood pressure and lipids. The prevalence of obesity in the United States and other Western countries has been steadily rising over the past two decades, a trend that has been linked to changing dietary habits and sedentary lifestyle (5-7) and that shows no signs of abating yet. This increased prevalence has been reported in both children and adults (5). According to the National Health and Nutrition Examination Survey, the prevalence of obesity (defined as BMI>30 kg/m²) has increased from 14.1% to 22.5% between 1971 and 1994 and to 30.5% in 2000. Currently, 64.5% of the adult US population is overweight (BMI>25 kg/m²) (8). The situation in the Netherlands is not as bad as in the USA, but nevertheless 40% of the population is overweight - 25% of them is obese, resulting in a prevalence of 10% obesity. The rise in weight excess is especially concerning in children, and in particular for those of Maroccan or Turkish descent, for whom the percentages of being overweight and obese are more than twice the percentages in Dutch children of comparable age intervals (9). Health policies aim at reducing the incidence by prevention programs.

Obesity as a renal risk factor

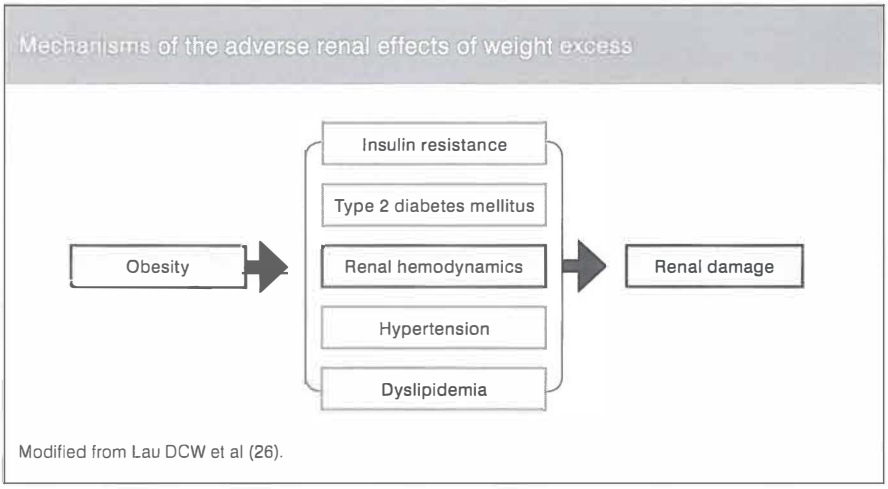
It has long been known that morbid obesity can, in rare cases, elicit proteinuric renal disease (10;11), in the absence of other (apparent) triggers for renal damage. Obesity is also a risk factor for renal damage in native kidney disease (11-13), in renal transplant recipients (14-19), and after uni-nephrectomy (20). In recent years however, it has become clear that the renal risks of obesity and overweight are much more widespread than previously assumed. Several population-based studies reported obesity to be a

significant and independent risk factor for long term renal function loss (21;22). A recent study by Hsu et al (23) provided further support for the detrimental influence of a higher BMI on long term renal function loss in the general population. Compared to people with a normal BMI (<25 kg/m²) the relative risk for end stage renal disease (ESRD)(adjusted for diabetes and hypertension) after 15 to 35 years of follow-up was 1.72 for those who were overweight (BMI 25-29 kg/m²), 2.98 for those with class I obesity (BMI 30-34.9 kg/m²), 4.68 for those with class II obesity (BMI 35-39.9 kg/m²) and 4.99 for those with a BMI higher than 40 kg/m². Corresponding results were reported by Ejerblad et al (24), in a long-term case-control study in over 900 Swedish subjects, who showed that a BMI over 25 kg/m² in otherwise healthy young men was associated with a 3–fold risk for end stage renal damage after long-term follow-up.
The Table shows the impact of overweight and obesity on the risk for renal insufficiency in the aforementioned and 3 other large population-based trials.

Table

Author	No. patients/population	BMI	Follow up	Outcome
Fox (21)	2585/community based	26.1	18.5 yrs	9.4% CKD stage 3, OR 1.23
Iseki (22)	100.753/general population	23.4 (17.9-59.1)	17 yrs	ESRD in 404 patients, OR 2.48 and 5.81 for lowest and highest quartile of BMI, respectively
Gelber (25)	11.104/healthy men	Analysis for quintiles	14 yrs	12.4% CKD stage 3, OR 1.45 in highest quintile of BMI
Ejerblad (24)	926/adults with CKD stage 4-5	25.6 (M), 25 (F)	retro-spective	3-fold risk for CRF among patients with overweight at age 20
Hsu (23)	320.252/adults volunteering for health check ups	24.5 (SD 4.3)	15-35 yrs	ESRD in 1471 cases, OR 1.72 and 4.99 for lowest and highest quartile of BMI, respectively

So, within little more than a decade, the perspectives of weight excess as a factor involved in the risk for renal damage has dramatically changed, from a rare renal condition in morbidly obese subjects to a highly prevalent and established risk factor for end stage renal function loss. Considering the epidemiology of weight excess, this is reason for concern from a renal perspective. If the increasing incidence of weight excess would translate into an increased renal risk with a time lag of 15 to 20 years, this would have major impact on the prevalence of end stage renal disease world wide, even taking into consideration the competing risk of elevated cardiovascular mortality that is likely to reduce the number of subjects that survive long enough to progress into end stage renal failure. Obviously, population health programs aimed at correction of weight excess should have high priority. Nevertheless, it would be overly optimistic to expect that this will eliminate weight excess as a renal risk factor. It would be important therefore, to better understand the mechanisms underlying the adverse impact of weight excess on the kidney in order to develop specific, renoprotective measures to reduce the renal risk associated with weight excess.



Modified from Lau DCW et al (26).

Several factors that are usually associated with obesity, such as hypertension, insulin resistance and diabetes, and possibly also dyslipidemia, are assumed to account for part of the increased renal risk in obesity (27-30). Yet, other factors specifically related to weight excess are likely to be involved as well.

The renal effects of obesity in experimental animals and humans include both structural and functional adaptations. The most accurately described type of renal involvement is the so-called 'obesity-related glomerulopathy', with slowly progressive proteinuria, which can reach the nephrotic range (10;31-33). The appearance of proteinuria usually precedes the onset of renal function decline by several years (10;31-33). The histological counterpart of these clinical manifestations include focal segmental glomerulosclerosis, and glomerulomegaly as the most significant and frequent findings (10;31;32). In this respect, Rea et al (34) recently studied implantation biopsies in 49 obese kidney donors, showing larger glomerular planar surface area compared to non-obese controls, correlating to patient weight and urinary microalbumin excretion. Of note, the obese donors had higher systolic blood pressure and higher absolute iothalamate clearance than the non-obese donors. Glomerular size however, did not correlate with total corrected or uncorrected glomerular filtration rate.

Functional changes in obesity include hemodynamic alterations, with glomerular hyperperfusion and hyperfiltration. An increase of glomerular filtration rate (GFR), effective renal plasma flow (ERPF), glomerular filtration pressure and filtration fraction (FF) through a dilated glomerular afferent arteriole, accompanied by a relatively elevated efferent arteriolar vascular tone has been repeatedly, albeit not uniformly, found in experimental models of obesity (35-37) and human obesity (13;38). Glomerular hyperfiltration, and in particular glomerular capillary hypertension has extensively been shown to be a driving force for progressive renal function loss in remnant kidney models by glomerular capillary damage, resulting in glomerular protein leakage and nephron loss, thus eliciting a vicious circle of progressive renal damage (39). In obesity models, the evidence for a pathogenetic role of glomerular hypertension is not as abundant as in remnant kidney models. Its relative contribution to overall renal damage, versus the effects of systemic hypertension, insulin resistance and dyslipidemia has not been fully elucidated with certainty, and may in fact vary among the different obesity models.

In human obesity the renal hemodynamic profile strongly resembles the hyperfiltration pattern in diabetes. An elevated GFR is consistently found, with an increase in ERPF that is either proportional, or somewhat less, resulting in a FF that is either normal or elevated. In the former case, the driving force for the elevated GFR seems to be glomerular hyperperfusion, in the latter glomerular capillary hypertension (40). As this

pattern is, at least partly, reversible after rigorous weight loss functional changes are apparently involved.

In diabetes hyperfiltration has been shown to precede the onset of nephropathy and is generally assumed to be a pathogenetic factor in the progression of renal damage (41-43). It should be mentioned however, that in human the evidence for an independent pathogenetic role of renal hemodynamics is of an indirect nature (44;45) as there are no prospective longitudinal data on the independent effect of the renal hemodynamic profile on long term renal outcome. Yet, the proven pathogenic potential of glomerular hypertension in animal models, together with the similarity to the renal hemodynamic profile in incipient nephropathy in diabetes fuel the hypothesis that renal hemodynamic factors, i.e. glomerular hypertension and hyperfiltration play a pathogenetic role in the long-term renal risk associated with weight excess.

Multiple factors are assumed to contribute to these renal hemodynamic alterations of obesity, such as inappropriate activity of the renin-angiotensin-aldosterone system (RAAS), the tubulo-glomerular feedback response to increased proximal sodium reabsorption, insulin resistance (27) and possibly also inappropriate activity of the sympathetic nervous system and increased leptin levels (46-48).

Renal hemodynamic measurements in human

Glomerular hemodynamics can be measured directly by micropuncture studies in rat strains where the glomeruli are located exceptionally close to the surface of the kidney. In human, however, renal hemodynamics can only be measured indirectly. Although currently duplex Doppler sonography is used to estimate renal blood flow in clinical conditions such as renal artery stenosis, the gold standard for renal hemodynamic evaluation is still the measurement of the renal clearance of specific tracers. Specific tracers for glomerular filtration rate, such as inulin or iothalamate, are characterized by being freely filtered, and are devoid of tubular handling and of extrarenal routes of excretion. Specific tracers for renal plasma flow, such a para-amino-hippuric acid and its derivatives, are characterized by complete renal extraction of the tracer by active tubular transport, to the effect that the rate-limiting factor for clearance is the delivery to peritubular capillaries, i.e. renal perfusion. In our centre accurate assessment of GFR and ERPF is performed on a routine base as the simultaneously measured clearances of ^{125}I-iothalamate and ^{131}I-hippurate, respectively, by the constant infusion method.

The simultaneous measurement has two distinct advantages. First, the plasma clearance of ^{131}I-hippurate has been shown to equal the renal clearance in case of perfect urine collection. Thus, the urine collection error can be derived from the ratio of the plasma-to-urinary clearance of ^{131}I-hippurate. This allows correcting for the voiding error for ^{125}I-iothalamate clearance, which considerably enhances the accuracy of the measurement of GFR (49). Moreover, when GFR and ERPF are measured simultaneously, filtration fraction (FF) can be calculated as the ratio from GFR and ERPF. FF serves as a helpful parameter to interpret changes in GFR in terms of the underlying hemodynamic changes. When a rise in GFR is primarily due to hyperperfusion, it will be associated with a proportional rise in ERPF and thus unaltered FF. When a rise in GFR is primarily due to a change in filtration pressure, this will be apparent as a rise in FF, as ERPF will be elevated less than GFR. As already mentioned above, an elevated filtration pressure is assumed to be a pathogenetic factor in long-term renal damage. For these reasons, FF can be considered a surrogate parameter for glomerular hypertension in man.

Several considerations should be taken in mind when evaluating renal hemodynamics in obesity by clearance methods. First, the pathophysiologically relevant issue is hyperfiltration at the single nephron level. Clearance measurements in human, however, reflect total filtration rate of all nephrons together, so a GFR within the normal range may reflect a normal filtration rate in a normal nephron number, but also an elevated filtration rate in a decreased number of nephrons without a possibility to distinguish between these conditions. Only if total GFR is elevated, glomerular hyperfiltration is present with certainty. Second, for comparison of renal hemodynamics between individuals GFR and ERPF are indexed for body dimensions, usually body surface area. However, when addressing possible renal effects of weight excess, this common practice could well induce a systematic error, as weight excess leads to a higher body surface area. Thus for obese individuals indexing would lead to lower renal function outcomes in comparison to subjects without weight excess. The validity of this approach is questionable, and several authors have recommended indexing for height (50-52), especially for the purpose of investigating effects of obesity. In this respect assessment of FF provides some specific advantages. First, as it is derived from both GFR and ERPF its interpretation is less affected by assumptions on nephron number. Moreover, it is not dependent on assumptions on the best way to index for individual differences. For these reasons, despite its indirect nature, FF is a highly useful parameter in the study of renal hemodynamics in relation to weight excess.

Aim of the thesis

This thesis addresses the relationship between weight excess and renal hemodynamics in human. Studies on the relationship between obesity and renal hemodynamics in humans are scarce, and mainly limited to morbid obesity, usually associated with insulin resistance, diabetes and/or hypertension (27;51;53). As recent data have shown that the impact of weight excess is not limited to morbid or even overt obesity, but also is relevant to milder forms of weight excess, the latter becomes a relevant topic for research as well, in particular for preventive purposes.

The University Medical Center in Groningen has some 30 years of history of accurately assessing renal hemodynamics by measuring the clearances of ^{125}I-iothalamate and ^{131}I-hippurate, as measures for GFR and ERPF, respectively (54). It is used for patient management in different settings of third-line referral populations, such as renal transplant recipients, potential kidney donors and lung transplant recipients, as well as for physiological studies in healthy volunteers. This setting provides the perfect opportunity to study the relationship between obesity, overweight and renal hemodynamics in different populations in more depth.

Renal function measurements

The gold standard for monitoring renal function is serial measurement of GFR. In clinical practice, however, this is not always feasible due to logistic, financial, or patient related problems. A more practical and cheaper way to measure renal function is by estimating GFR, making use of creatinine-based equations. It is known, however, that these equations can be biased by body dimensions. After renal transplantation body composition usually changes, possibly violating the assumptions underlying the renal function equations. In **Chapter 2** we test the predictive performance of 9 renal function equations in a large population of renal transplant recipients, with specific emphasis on the demographic determinants, including age, gender and body mass index on the systematic error, both for cross-sectional analysis and for long-term follow-up.

Renal hemodynamics

As noted above, altered renal hemodynamics with glomerular hyperfiltration was reported mainly in morbid obesity (13;38). As the risk for long-term renal function apparently occurs already at less severe degrees of weight excess, starting at a BMI

>25 kg/m², in the general population as well as in transplant recipients (17;18), it would be important to explore the possible mechanisms underlying the increased renal risk in moderate weight excess. So far, it has not been established whether a mild or moderate degree of weight excess is associated with altered renal hemodynamics as a candidate mechanism for long-term renal function loss. Furthermore, in morbid obesity hypertension and/or insulin resistance are usually simultaneously present, so it is uncertain whether documented renal hemodynamic abnormalities are due to the effects of hypertension, insulin resistance or their combination, or whether the weight excess has renal effects independent of these factors as well. Therefore, in **Chapter 3** we investigated the association between body mass index and renal hemodynamics in healthy adults, with a body mass index not exceeding 30 kg/m², and normal blood pressure, to see whether a higher body mass index would be associated with a renal hyperfiltration and/or hyperperfusion pattern.

Obesity and overweight of the recipient are associated with renal risk after transplantation as well. Whether this increased renal risk is due to altered renal hemodynamics, i.e., a hyperfiltration pattern in the transplanted kidney, has not been established. In fact, the impact of weight excess on renal hemodynamics in the transplanted kidney has not been established either. In this respect, we want to emphasize that it is not warranted to simply extrapolate data from native kidneys to transplanted kidneys, as multiple factors, such as cyclosporin use, the single kidney state, and presence of intrinsic renal damage all may affect hemodynamics in the transplanted kidney, and thus overrule possible weight-related factors. Moreover, as opposed to native kidneys, the transplanted kidney is denervated. Of note, the transplanted kidney also provides an interesting model system, where the genetic background of the kidney and the recipient are different. So for various reasons it would be relevant to establish whether a higher recipient BMI is associated with a specific renal hemodynamic profile. Moreover, it would be important to establish whether the association between high BMI and worse renal outcome in transplant recipients can be attributed to the renal hemodynamic profile. These questions are addressed in **Chapter 4**, describing the cross-sectional association between BMI and renal hemodynamics in transplant recipients, as well as long term outcome data, in relation to BMI and renal hemodynamics, respectively.

As noted above, for the purpose of detecting hyperfiltration the interpretation of whole kidney clearance measurements can be cumbersome and hyperfiltration at the single

nephron level cannot be excluded if GFR is normal or decreased. Therefore, additional strategies have been developed to address the issue of hyperfiltration. These strategies start from the assumption that a decrease in filtration reserve is a sign of hyperfiltration. The normal kidney has a considerable filtration reserve, as for instance apparent from the immediate rise in GFR and ERPF in the remaining kidney after donation, from the considerable rise in GFR and ERPF in pregnancy, and from the responses to several renal vasodilators. Several protocols have been developed to assess the reserve of filtration and perfusion, respectively, from the renal responses to specific renal vasodilators, alone or in combination (55-57). In our centre, the renal responses to dopamine, amino acids and their combination have been routinely in use for a long time for this purpose. Dopamine elicits preferential efferent vasodilation (resulting in a rise in ERPF that exceeds the rise in GFR), whereas amino-acids give predominantly afferent vasodilation, resulting in a prominent rise in GFR, with a less prominent or unchanged ERPF. The combination of the two gives both afferent and efferent vasodilation and marked increases in GFR and ERPF that exceed those with the two separate compounds. Renal reserve filtration capacity may be relevant for maintenance of renal function after loss of functional renal mass by disease, or after kidney donation. In this concept, loss of nephrons, by for instance kidney donation, or by the aging process, would be associated with reduction of renal reserve capacity by using the available reserve for maintenance of renal function. Moreover, hyperfiltration could be hypothesized to be unmasked by a loss of reserve capacity, and accordingly absence or decrease of filtration reserve could be a marker of sustained single nephron hyperfiltration that may have maladaptive consequences by damaging remnant glomeruli. To see whether the renal hemodynamic pattern associated with weight excess might reflect hyperfiltration, in **Chapter 5** we investigated the association between BMI, renal hemodynamics and renal reserve capacity. The hypothesis to be tested was that a higher BMI would be associated with a decrease in reserve capacity. The impact of other possible factors that might decrease reserve capacity, such as older age, and loss of nephrons by uninephrectomy was addressed as well. To this purpose we measured renal hemodynamics and renal reserve capacity before and after kidney donation, with analysis for determinants of reserve capacity.

General discussion and summary

In **Chapter 6** we provide an overview of the current literature on the impact of obesity and overweight on renal hemodynamics, putting the findings from our own studies in a broader perspective. We discuss potential underlying mechanisms, implications for long-term renal risk and possible strategies for intervention.

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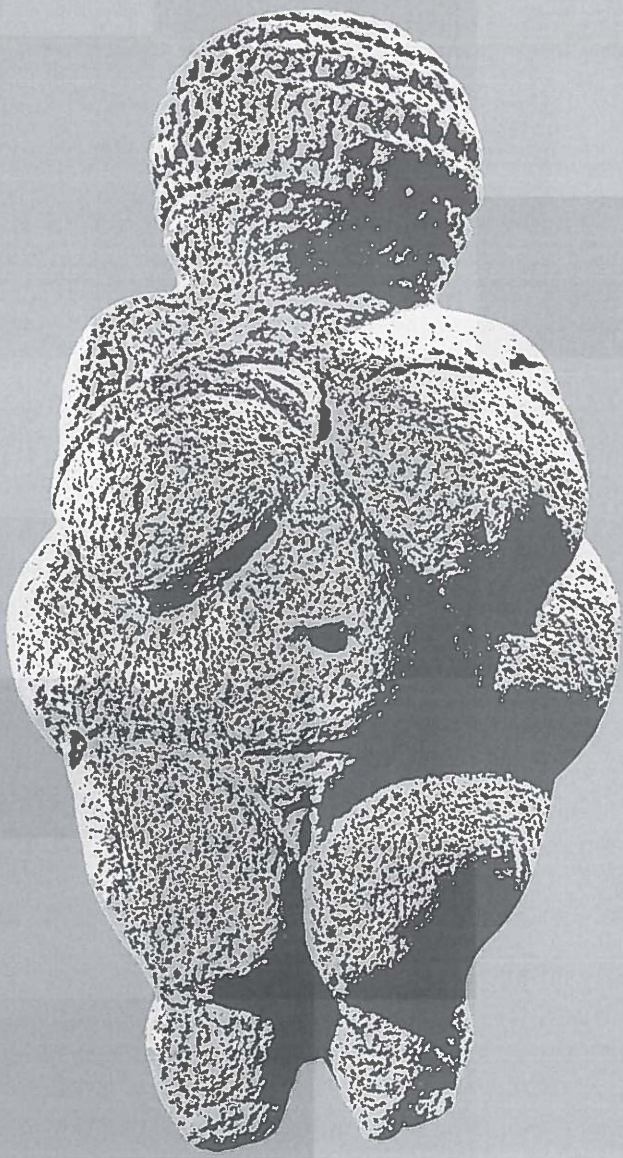

Chapter 2

Predictive performance of renal function equations in renal transplant recipients:

an analysis of patient factors in bias

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Abstract

Background. Creatinine-based equations are available to estimate GFR. After renal transplantation body composition usually changes, thus specific validation is required for transplant recipients.

Methods and results. Nine equations were compared with iothalamate GFR at 1 year after transplantation in 798 recipients. Equations were analyzed for precision, bias and accuracy. Sources of bias were analyzed by uni- and multivariate analysis, with body mass index (BMI), age and sex as independent variables and bias as dependent variable. Four hundred and seventy-eight patients were studied to assess whether the equations can be used to monitor renal function over time. Predictive performance was modest for all equations. MDRD and Jelliffe 2 were the best predictors of GFR. Bias was significantly related to BMI, age and gender in most equations. Multivariate analysis confirmed their independent contribution to the bias of MDRD, Jelliffe 2, and most other equations. Over time, bias was relatively stable at group level, but predictive performance in individuals was modest.

Conclusions. The predictive performance of renal function equations is modest in renal transplants, which hampers their use for accurate assessment of renal function in the individual. The role of patient factors in the systematic error suggests that development of better equations should be feasible by better incorporation of these factors.

Introduction

Glomerular filtration rate (GFR) can be precisely measured by specific filtration markers such as inulin, ^{125}I-iothalamate, ^{51}Cr-EDTA, ^{99m}Tc-DTPA and iohexol. These measurements, however, are laborious and expensive, and therefore, in clinical practice GFR is usually estimated from serum creatinine, using renal function equations that include antropometric indices such as age, weight and gender to account for between-individual differences in muscle mass and the consequent differences in creatinine generation. Many equations are available, most of which were developed in populations with native kidney disease (1-18). The predictive performance as well as the shortcomings of creatinine-based renal function equations have been subject of several recent reviews (19;20).

After renal transplantation body composition often changes, with a high prevalence of obesity and loss of muscle mass due to steroid use - which could violate the assumptions underlying the creatinine-based renal function equations. Thus, for renal transplant recipients specific validation of renal function equations would be required. Several studies addressed this issue (21-25), indicating a relatively poor predictive performance of renal function equations in the transplant population. However, these studies included only relatively small populations, and only evaluated a small number of equations. Furthermore, in these studies the factors underlying the poor predictive performance, and the consequences for the clinical monitoring of individual patients over time were not analyzed. In the present study, therefore, we studied the predictive performance of nine renal function equations in a large single center population of renal transplant recipients, and analyzed for determinants of the systematic error. Moreover, to assess the suitability of equations to monitor renal function over time, the stability of bias over time, and the accuracy of the equations to predict the change in GFR over time were studied in 478 patients with a follow-up to 5 years after transplantation.

Methods

Patients

The study group consisted of 798 renal transplant recipients (722 from cadaveric and 77 from living donors, 453 males, 345 females, mean age at transplantation: 44±13

years) in whom renal hemodynamic measurements had been routinely performed in our department 1 year after transplantation. The patients were transplanted between 1984 and 2002. The study group was selected out of 1798 patients - the total number transplanted from 1968 until 2002. Of 997 patients renal hemodynamic measurements at 1 year after transplantation were available. Of these patients, 199 could not be included because relevant data on certain hemodynamic parameters were missing. The routine immunosuppressive regimen is described in detail elsewhere (26).

Methods

Renal hemodynamic measurements

Glomerular filtration rate (GFR) was measured by constant infusion of ^{125}I-iothalamate, with correction for voiding errors by simultaneous measurement of the clearance of ^{131}I-hippuran as described by Donker et al and Apperloo et al (27;28). Briefly, an intravenous canula was inserted for tracer infusion at 8 a.m. The infusion fluid consisted of 4 MBq ^{131}I-hippuran and 3 MBq ^{125}I-iothalamate per 100 mL saline. First, a priming solution of 0.4 mL/kg body weight was administered plus an extra 0.6 MBq ^{125}I-iothalamate to ensure steady state of the plasma tracers within the time frame of the measurement. Thereafter, a continuous infusion was started. After a stabilization period of 2h, two 2-h clearance periods followed. GFR was measured as the urinary clearance of ^{125}I-iothalamate (UV/P) and corrected for voiding errors by multiplying UV/P_{iothal} by the ratio of plasma clearance of ^{131}I-hippuran to urinary clearance of ^{131}I-hippuran. This correction method is based on the fact that, during steady state, the plasma clearance of ^{131}I-hippuran equals its urinary clearance when urine collection is perfect. Thus, the voiding error is can be calculated from the ratio of urinary clearance and plasma clearance of ^{131}I-hippuran. This GFR measurement has a day-to-day coefficient of variation of 2.2%. Serum creatinine levels were determined by an alkaline picrate creatinine assay (Jaffé), which has a day-to-day variability of 4% in our laboratory.

Renal function equations

As a first, screening, step, 18 equations (Cockcroft, Edwards, Mawer, Bjornsson, Hull, Salazar, Nankivell 1 (developed for kidney transplant recipients), Nankivell 2 (developed for combined kidney/pancreas transplant recipients), Baracskay, Walser, Jelliffe 1* and 2*, Gates*, Agarwal*, Toto*, Nguyen*, simplified MDRD* and the recently published

equation developed by Rule* et al (1-18) were analyzed for predictive performance from the data obtained at 1 year after transplantation.

These equations are given in Appendix 1. Equations were analyzed for precision (R^2, defined as the scatter of the series of observations), accuracy (defined as the percentage of subjects within 30% of true GFR, i.e ^{125}I-iothalamate clearance) and bias (calculated as the mean prediction error (ME), defined as ME = 1/N Σ (predicted value - true value). All equations were tested against true GFR, including equations predicting creatinine clearance. Equations predicting GFR per BSA (indicated by *) were tested against GFR per BSA. Walser and Hull were tested against GFR per 3 m^2 and GFR per 70 kg respectively.

Selection of equations for detailed analysis

A selection of the equations was used for further analysis. The MDRD, Jelliffe 2, Jelliffe 1, Gates, Cockcroft, Hull and Mawer were selected because they are reviewed in six papers or more (a criterion also used in the DOQI guidelines review on the use of renal function equations (20)) and in our population had an overall predictive performance (30% accuracy) above 70%. Nankivell 1 was chosen because it was especially developed for the renal transplant population. Finally, we included the recently published equation of Rule et al (15), as this equation is anticipated to provide a better renal function estimate in subjects with mild renal function impairment.

The 10 and 30% accuracy of the non-selected equations was: Salazar: 31 and 71%; Bjornsson: 33 and 70%; Agarwal 17 and 51%; Toto 18 and 50%; Baracskay 15 and 39%; Nguyen 4 and 13%; Edwards: 36 and 85 %; Walser 30 and 82 %; Nankivell 2: 30 and 80%, respectively. The sources of systematic error in these non-selected equations were comparable to those of the selected ones, but for the sake of conciseness these data are not presented in the paper.

Predictive performance over time

The suitability of equations to monitor renal function over time was tested in all 478 subjects in whom data were available at 2 and 5 years as well, in addition to data at 1 year after transplantation. First, the mean bias at years 1, 2 and 5 was calculated and tested for changes over time. Second, to test the suitability for follow-up we assessed the predictive performance of the equations to detect a change in true GFR over time (R^2, bias, accuracy).

Statistical analysis

Statistical computations were performed using SPSS, version 12.0 software (SPSS Inc., Chicago, IL, USA). To test for the sources of the systematic error univariate and multivariate analysis was performed. For univariate analysis the population was divided in tertiles of BMI, age and GFR, respectively. The difference in bias between the tertiles was assessed by analysis of variance (ANOVA). The difference in bias between men and women was tested by ANOVA as well. Multivariate analysis was used to identify patient characteristics that were independent determinants of the systematic error. This was analyzed by multilinear regression analysis, with bias as the dependent variable and BMI, age and sex as independent variables. To test whether bias changed over time, repeated measures analysis by general linear modeling was performed in the subgroup with a follow-up to 5 years after transplantation, with bias as the dependent variable. A two-sided p-value less than 0.05 was considered statistically significant.

Results

Overall predictive performance

Patient characteristics are given in Table 1. Mean body mass index (BMI) was 25.6 (±4.0) kg/m². Obesity (BMI>27.0 kg/m²) was present in 32% of the patients (n=252). Table 2 presents the overall predictive performance of the nine selected equations, calculated from the data at one year after transplantation. Predictive performance is expressed as precision (R^2, depicted for individual patients in Figure 1), bias (the mean prediction error) and 10% and 30% accuracy (the % of values within 10% and 30% of the true value, respectively), ranked by 30% accuracy. It shows, first, that the non-systematic error, as reflected by the precision, is relatively large for all equations. Second, the average systematic error, i.e. bias or prediction error, appears small for most formula, with small confidence intervals as well, probably due to the large number studied. However, the standard deviation of the prediction error is large. This implicates that for individual patients the estimates can be highly inaccurate. Finally, the predictive performance of creatinine clearance measured by 24-h urine collection, was worse than for the tested equations.

Table 1 Population characteristics (n=798)

	Mean±SD	Range
Male/female 453/345		
Age (years)	44±13	14-77
BMI (kg/m²)	25.6±4.0	15.8-46.6
MAP (mmHg)	108±12	73-167
GFR (mL/min)	55±18	18-115
Serum creatinine (μmol/L)	145±40	68-267
Creatinine clearance (mL/min)	64±21	16-146

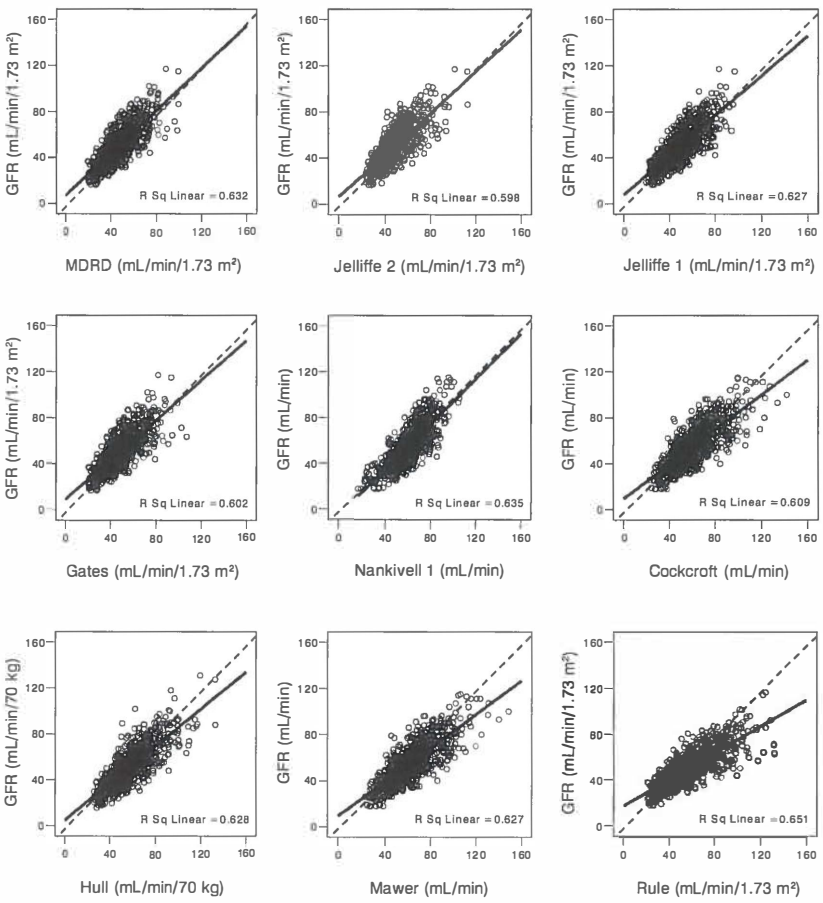
Table 2 Overall predictive performance, ranked by 30% accuracy

Formula	Precision	Bias	95% CI	Range	Accuracy	
					10%	30%
MDRD	0.63	-3.2	-3.9/-2.5	-30.4/35.5	38%	88%
Jelliffe 2	0.60	-1.4	-2.1/-0.7	-37.7/30.9	36%	88%
Jelliffe 1	0.63	-0.9	-1.6/-0.2	-33.2/38.0	37%	87%
Gates	0.60	-1.6	-2.4/-0.9	-34.6/44.8	40%	87%
Nankivell 1	0.64	5.8	5.1/6.8	-28.0/39.8	35%	76%
Cockcroft-Gault	0.61	6.3	5.4/7.1	-34.6/50.3	36%	76%
Hull	0.63	6.5	5.7/7.2	-39.5/45.0	35%	74%
Mawer	0.63	7.4	6.6/8.2	-33.6/50.0	35%	73%
Rule	0.65	7.4	6.5/8.3	-4.7/68.5	29%	72%
Creatinine clearance	0.55	9.3	8.3/10.3	-37.0/83.0	23%	66%

Sources of systematic error

As apparent from Figure 1, for most equations the prediction error is not stable over the different levels of true GFR. We quantified this by comparing the prediction errors for tertiles of true GFR for all equations as shown in Figure 2. Bias was significantly and considerably different for the different tertiles of GFR for all equations. Remarkably, for the Rule equation the impact of the level of GFR on bias was opposite to that of all other equations.

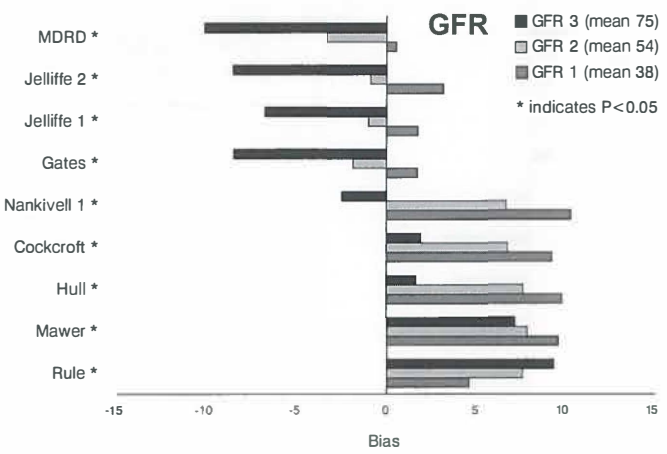
Figure 1 Correlations between selected equations and true GFR



Scatter plots, showing the correlations between the selected equations and the measured GFR. The dashed lines represent the lines of identity.

The impact of BMI, age and gender, respectively, on the systematic error is shown in Figures 3a-c. Figure 3a shows mean values for bias for all equations (ranked by 30% accuracy) by a break-up according to tertiles of BMI. Mean BMI for the increasing tertiles was: 21.7 (range 15.8-23.7), 25.3 (range 23.7-26.8) and 30.0 (range 26.8-46.6) kg/m². It shows that BMI significantly affects bias in all but three equations. It is also

Figure 2 Mean bias for tertiles of GFR



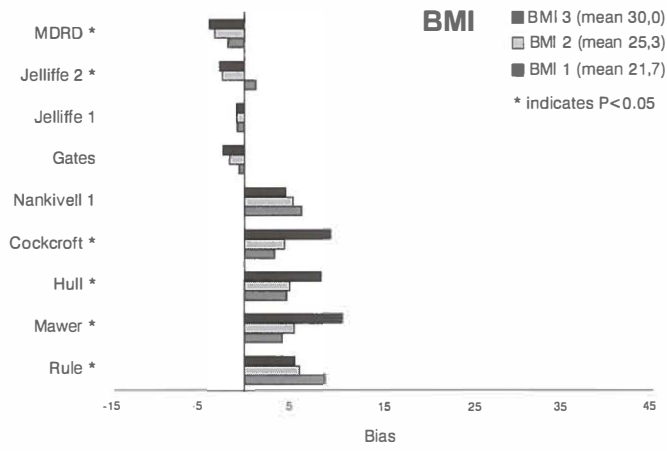
Univariate analysis showing the mean values for bias (mL/min) for the selected equations (ranked by 30% accuracy) by a break-up according to tertiles of GFR.
GFR 1: 38 (range 18-46) mL/min
GFR 2: 54 (range 47-61) mL/min
GFR 3: 75 (range 62-115) mL/min
* Bias significantly different across the tertiles (ANOVA, $p<0.05$).

Table 3 Multivariate analysis

		BMI		Age		Sex	
	R^2	Beta	P	Beta	P	Beta	P
MDRD	0.073	-0.121	0.001	-0.007	0.832	0.241	<0.001
Jelliffe 2	0.171	-0.102	0.002	-0.356	<0.001	-0.134	<0.001
Jelliffe 1	0.115	-0.118	0.001	0.329	<0.001	-0.930	0.005
Gates	0.149	-0.112	0.001	0.006	0.870	0.371	<0.001
Nankivell 1	0.101	-0.167	<0.001	0.282	<0.001	0.128	<0.001
Cockcroft	0.266	0.393	<0.001	-0.423	<0.001	0.078	0.010
Hull	0.206	0.279	<0.001	-0.425	<0.001	0.032	0.318
Mawer	0.248	0.404	<0.001	-0.396	<0.001	0.017	0.587
Rule	0.044	-0.118	0.001	-0.108	0.003	-0.114	0.001

Table showing the models for the different equations obtained by multilinear regression analysis.
All models were statistically significant.

Figure 3a Factors involved in bias



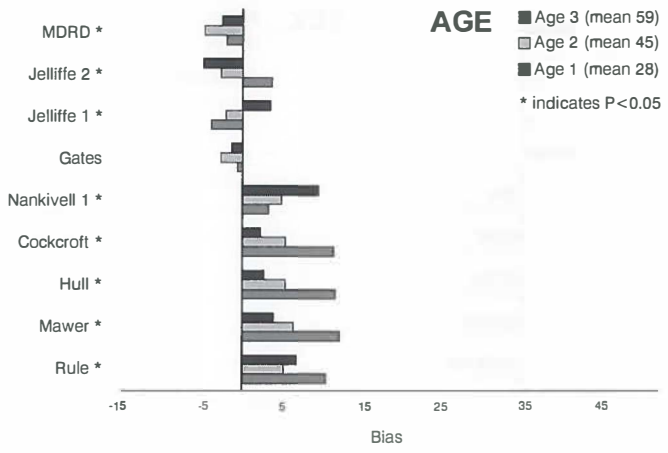
Univariate analysis showing the mean values for bias (mL/min) for the selected equations (ranked by 30% accuracy) by a break-up according to tertiles of BMI.
BMI 1: 21.7 (range 15.8-23.7) kg/m²
BMI 2: 25.3 (range 23.7-26.8) kg/m²
BMI 3: 30.0 (range 26.8-46.6) kg/m²
* Bias significantly different across the tertiles (ANOVA, $p<0.05$).

apparent that the effect of BMI on bias for the two most widely used equations, the MDRD equation and the Cockcroft-Gault equation, is opposite, with underestimation of GFR at high BMI by the MDRD, and overestimation of GFR at high BMI by the Cockcroft-Gault equation.

Figure 3b shows bias by a break-up according to age. Mean age per tertile was 28.4 (range 14-38) years, 45.3 (range 39-51) years and 58.8 (range 52-77) years, respectively. Again, in all but one equation the systematic error is significantly affected by age. Finally, Figure 3c gives mean bias by a break-up according to gender, showing that gender has a significant effect on bias in most equations.

Multivariate analysis was performed to see whether the patient characteristics BMI, age and sex were independent determinants of the prediction error, or whether there might be interdependency. An outline of the models is given in Table 3, showing that BMI was

Figure 3b Factors involved in bias



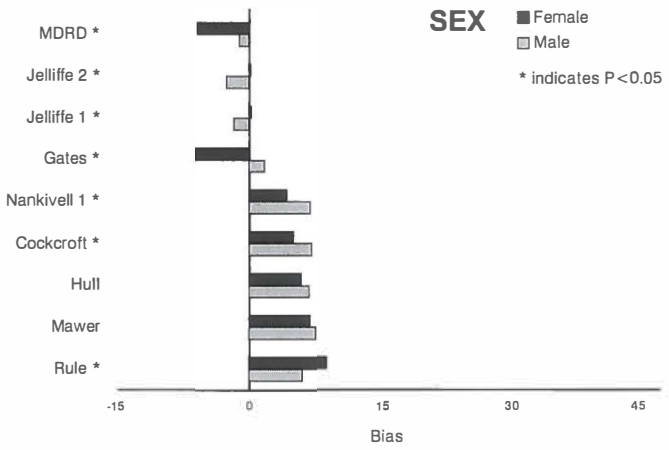
Univariate analysis showing the mean values for bias (mL/min) for the selected equations (ranked by 30% accuracy) by a break-up according to tertiles of age.
Age 1: 28.4 (range 14-38) years
Age 2: 45.3 (range 39-51) years
Age 3: 58.8 (range 52-77) years
* Bias significantly different across the tertiles (ANOVA, $p<0.05$).

an independent determinant of the model explaining bias for most equations, age for all but two equations, and gender for all but two equations.

Predictive performance to monitor renal function over time

To test the suitability of renal function equations to monitor renal function over time, first, in 478 recipients in whom GFR was also measured at 2 and 5 years after transplantation, we analyzed the course of the prediction error over time. Mean values for bias (±SE) at 1, 2 and 5 years after transplantation are given in Figure 4 (continuous lines). As the cross-sectional analysis at year 1 had shown that GFR and the BMI were determinants of the prediction error, we also evaluated whether the mean prediction error might be more stable over time in the subgroups with stable GFR (less than 10% change, n=215, broken lines) and stable BMI (less than 5% change, n=343, dotted lines), respectively. For the whole patient group, generally, the mean bias was fairly stable over time, not exceeding an absolute value of 2-3 mL/min over the 4-year

Figure 3c Factors involved in bias

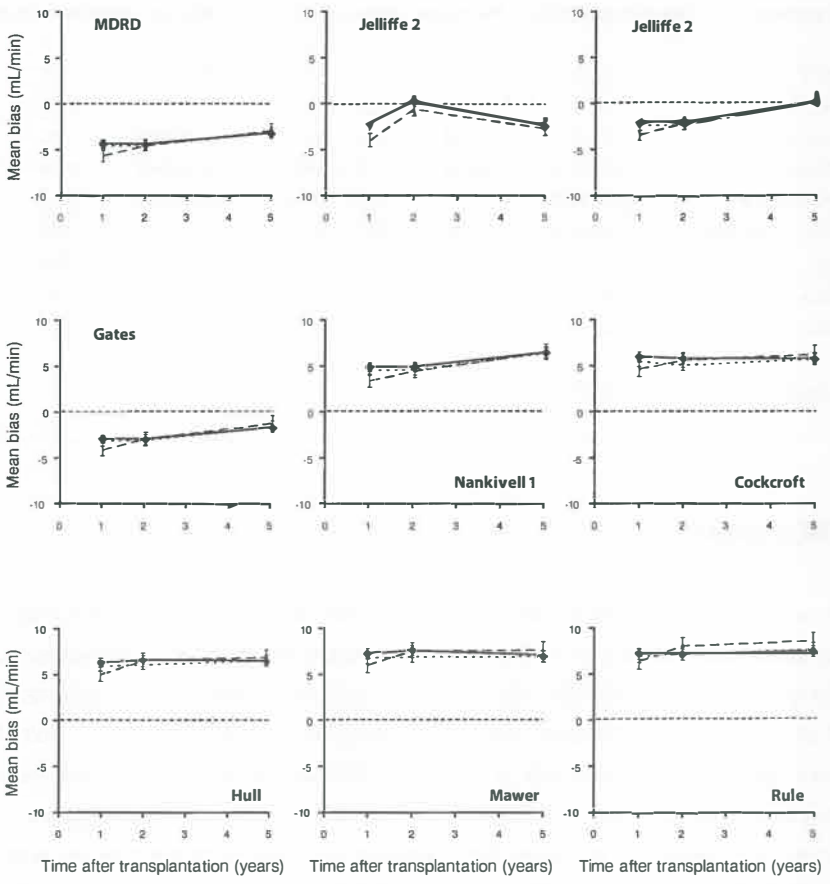


Univariate analysis showing the mean values for bias (mL/min) for the selected equations (ranked by 30% accuracy) by a break up according to gender.
* Bias significantly different across the tertiles (ANOVA, $p<0.05$).

observation period. On repeated measurement analysis, nevertheless, the small change in prediction error over time reached statistical significance for the MDRD, Jelliffe 1 and 2, Gates and Nankivell equations (all $p<0.001$). This was similarly true for the subgroups with stable BMI and stable GFR, respectively ($p<0.001$). For the Cockcroft-Gault, Hull, Mawer and Rule equation, bias did not change significantly over time.

Finally, we analyzed the accuracy of the equations in predicting the change in GFR over time. The mean change in GFR between years 1 and 5 was –1.9±15.1 mL/min (Table 4), whereas the mean changes estimated by the different equations ranged from +0.5± 12.1 mL/min (Jeliffe 1) to –2.3±12.3 mL/min (Hull), which was not significantly different from the change in true GFR. However, the precision of the equations to predict a change in true GFR from a change in estimated GFR was relatively poor, ranging from an R^2 of 0.49 (MDRD, Jelliffe 1, Gates and Hull) to 0.54 (Nankivell 1, Cockcroft-Gault and Mawer). Whereas mean bias was small, the confidence intervals were wide, and overall predictive performance was poor with a 30% accuracy that did not exceed 24% (Mawer). Data for individual patients are given in Figure 5, providing the correlations of the % change in true GFR with the % change in equation-estimated GFR, and with %

Figure 4 Differences between estimated GFR and true GFR (bias) at years 1, 2 and 5



Graphs showing mean bias (mL/min, ±SE) at years 1, 2 and 5. Continues lines: mean values for all 478 patients of whom hemodynamic measurements were available at years 1, 2 and 5. Broken lines represent the subpopulation with a stable GFR (n=215), dotted line represents the subpopulation with a stable BMI (n=343). The dashed line indicates the zerovalue for bias, so values above the dashed line implicate that the equation overestimates true GFR, and values below the line that the equation underestimates true GFR.

change in reciprocal of serum creatinine, respectively. It shows a relatively wide scatter of individual values, with R^2 values for the equations ranging from 0.49 (Rule) to 0.57 (Cockcroft-Gault and Mawer). For the reciprocal of serum creatinine the R^2 (0.51) was also within this range.

Table 4 Predictive performance of the changes between estimated GFR and true GFR (mL/min) at years 1 and 5

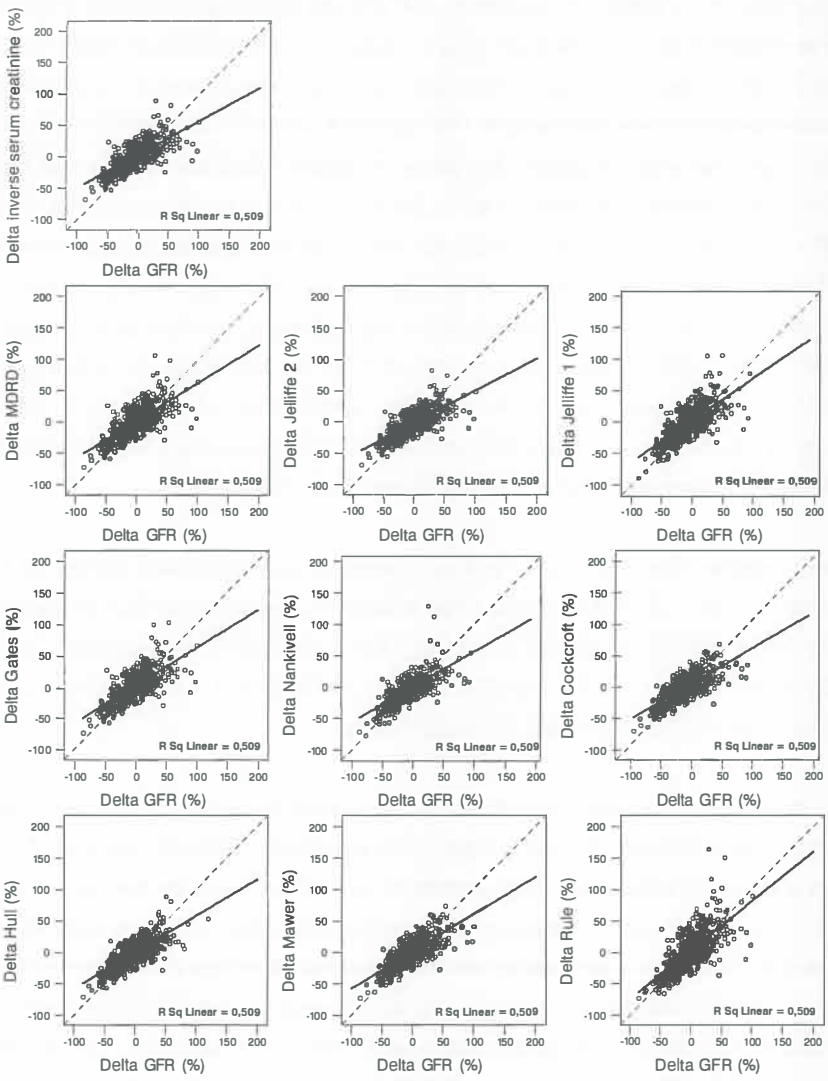
Equation	Delta (mean±SD)	Precision	Bias	95% CI	Range	30% Accuracy
MDRD	-0.5±10.9	0.49	1.1	0.2/2.0	-38.2/35.3	21%
Jelliffe 2	-1.9±9.8	0.50	-0.3	-1.2/0.6	-36.1/29.7	20%
Jelliffe 1	0.5±12.1	0.49	2.2	1.2/3.1	-39.0/38.0	21%
Gates	-0.5±11.3	0.49	1.2	0.3/2.1	-40.5/35.9	22%
Nankivell 1	0.3±12.0	0.54	1.6	0.6/2.5	-41.1/33.3	22%
Cockcroft-Gault	-1.4±13.4	0.54	0.4	-0.5/1.4	-47.3/42.4	22%
Hull	-2.3±12.3	0.49	0.1	-0.7/1.0	-40.0/28.4	22%
Mawer	-1.9±14.2	0.54	-0.1	-1.0/0.9	-49.9/43.9	24%
Rule	-1.4±17.1	0.44	0.3	-0.9/1.4	-51.4/41.3	20%
Iothalamate GFR	-1.9±15.1					

Discussion

The overall predictive performance of renal function equations in our renal transplant population was modest to poor. On group level, predictive performance was acceptable for several equations, but individual assessment of renal function was relatively poor for all equations, which hampers the use of equations in clinical practice, both for cross-sectional assessment and for long term follow-up. On univariate and multivariate analysis the patient characteristics age, gender and BMI were significant determinants of the systematic error. Moreover, the systematic error was dependent on the level of true GFR. As the systematic error can in principle be corrected for, these data indicate that it should be feasible to develop more accurate renal function equations.

Our study provides the largest transplant population analyzed so far. Several prior smaller studies recently evaluated the performance of specific renal function equations in transplant populations, with a comparable outcome as to overall predictive performance (21-25). At variance with these prior studies, the sample size of our population allows for analysis of the determinants of bias. This is relevant, as, in contrast to the random error, the systematic error can in principle be corrected for. Patient characteristics were involved in the systematic error in all equations, including

Figure 5 Correlations between % change in true GFR between years 1 and 5 and the % change in equation-estimated GFR, and the % change in reciprocal of serum creatinine



Graphs showing correlations between % change in true GFR (X-axes) between years 1 and 5 and the % change in equation-estimated GFR, and the % change in reciprocal of serum creatinine over that period for the 478 patients of whom iothalamate clearances were available at years 1, 2 and 5.

those with the best predictive performance. The patient characteristics age and gender are components of all equations, representing factors that modify muscle mass and hence creatinine generation and serum creatinine for a given renal function. Our analysis suggests, however, that the available equations do not adequately account for this relationship in the transplant population. BMI affected predictive performance as well. We analyzed for its impact as body weight is used in most equations to reflect muscle mass, without however, taking into account the impact of obesity on the estimation of muscle mass for a given body weight. The role of BMI as a determinant of the systematic error, therefore, was anticipated. It may be of clinical relevance that the two most widely used equations, the MDRD and the Cockcroft-Gault, had opposite effects on the BMI-related error in renal function estimate, with progressive underestimation at higher BMI by the MDRD, as compared to progressive overestimation of renal function at higher BMI by the Cockcroft-Gault equation. The systematic error was also dependent on the level of GFR. These data in transplant recipients are well in line with a recent analysis in a large population of European renal patients (without transplant recipients) showing that the biases of the MDRD and Cockcroft-Gault equations were significantly different for subgroups of age, gender, BMI and level of GFR (29).

Taken together, the impact of simple and generally available patient factors on the systematic error indicates that it should be feasible to develop a renal function equation with better predictive performance, by more adequately incorporating these demographic factors into the equation. This should be subject of future analysis, with probably an even larger number of measurements.

Our data derive from a single academic center and were obtained from the routine renal hemodynamic measurements in our transplant population. GFR was measured as the clearance of ^{125}I-iothalamate, with correction for voiding errors by the clearance of simultaneously infused ^{131}I-hippuran. This method has a day-to-day variability of only 2.2% (27). The single center set-up has the additional advantage of a uniform method for creatinine assessment, for which the day-to-day variability is 4%. We did not attempt to calibrate our creatinine measurements against that of other laboratories, as, in order to be valid, this should have been done for all different laboratories where the equations were originally developed, which was not feasible. Nevertheless, whereas the nominal values of estimated GFR might be somewhat modified by a different creatinine assessment, our data allow a comparative assessment of the equations in single center

setting, and a solid assessment of the predictive performance over time. The impact of calibration of serum creatinine measurements was recently re-emphasized by data by Hallan et al (30). In their study the MDRD equation underestimated GFR in a population with mild renal insufficiency, however, after recalibrating their serum creatinine values the systematic error was reduced and accuracy improved. This suggests that calibration of serum creatinine provides another possibility for better performance of renal function equations. It moreover illustrates a possible pitfall when the performance of an equation that has been developed in a specific population is tested in another one. In our analysis, for instance, the predictive performance of the MDRD equation, as well as of the Rule equation, lagged behind their performance in the original publications. This may be due to calibration factors, but also to differences in population characteristics (such as the ones identified here as confounders, but possibly also unidentified ones). The need to test even well-validated equations in other, large populations in order to be able to assess their generalizability has therefore been emphasized (20).

As to the clinical applicability of renal function equations, a distinction can be made between the assessment of group data and individual renal function assessment. In clinical epidemiology and clinical trials, the random error can be compensated for by larger patient numbers. The systematic error unfortunately cannot be accounted for by larger numbers. However, as to the bias induced by patient factors such as age and gender, the error can hopefully be distributed equally over the different patient groups, as randomization of patients usually takes into account age and gender. Our data indicate that for studies using renal function equations it would be useful to ensure that also BMI and level of GFR are equally distributed over the patient groups. For epidemiological purposes, recent data from our group, obtained in the general population, illustrate the impact of the error inherent to patient characteristics for the outcome of renal epidemiological studies using different renal function equations (31). For individual renal function assessment the problem of an accurate estimate was stated to be even larger, as underlined by several recent studies in different populations (32;33). Accordingly, these authors recommend not to rely on renal function equations for individual assessment, but to perform a true GFR instead, which is fully in line with our data in the transplant population.

We also evaluated the performance of the equations over time. At group level the mean change in GFR over a period of 4 years was well-reflected by all tested equations. This

is somewhat at variance with recent data by Gaspari (21). In a population of 81 transplant recipients they found that the rate of GFR decline between 6 and 21 months after transplantation was significantly higher for the tested equations than for the reference method, iohexol clearance. The reasons for the discrepancy with our findings are not immediately apparent, but may relate to differences in reference method, time elapsed after transplantation, or differences in patient population. Our data suggest that, within the time frame tested, renal function equations can be of use for follow-up of renal function in transplant recipients on the level of group data, provided that the sample size is sufficiently large. Obviously, for longer follow-up additional validation would be needed. Unfortunately, for individual follow-up of renal function over time the performance of renal function equations was disappointing. This could raise the question whether, for individual monitoring of renal function, the equations have any added value over serum creatinine only. In this respect our data showed that the correlation between % change in reciprocal of serum creatinine with the % change in GFR was more or less similar to that of most tested equations, refuting an added value of the equations for individual monitoring.

We conclude that the predictive performance of renal function equations is modest in the transplant population as a whole. For the best performing equations, the observed accuracy can be considered acceptable for, for instance, comparative clinical trials, provided that sample size and randomization allow for an equal distribution of the sources of systematic error (age, sex, BMI and GFR) over the groups. For individual patients however, the relatively low accuracy hampers accurate assessment of renal function by the tested equations, also for individual follow-up. Finally, the role of the systematic error indicates that better incorporation of body dimensions, age and gender will allow to develop better renal function equations with a better predictive performance in the renal transplant population.

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Appendix I Equations Used in the Article

Screat = serum creatinine (mg/dL)
Pcreat = serum creatinine (mmol/L)
Urea = serum urea (mmol/L)
BW = body weight (kg)
Ht = height (m)
Height = height (cm)
BMI = kg/m²

Baracskay et al (mL/min)
4,420/pcreat + 88 – age

Bjornsson (mL/min)
Male: {[27 - (0.173 * age)] * BW * 0.07}/screat
Female: {[25 - (0.175 * age)] * BW * 0.07}/screat

Cockcroft-Gault (mL/min)
Male: [(140 - age) * BW]/72 * screat
Female: correction factor 0.85

Edwards and Whyte (mL/min)
Male: (94.3/screat) - 1.8
Female: (69.9/screat) + 2.2

Hull (mL/min/70 kg)
Male: [(145 - age)/screat] - 3
Female: correction factor 0.85

Mawer (mL/min)
Male: {weight * [29.3 - (0.203 * age)] * [1 - (0.03 * screat)]}/(14.4 * screat)
Female: {weight * [25.3 - (0.175 * age)] * [1 - (0.03 * screat)]}/(14.4 * screat)

Nankivell 1 (mL/min)
Male: 35 + 6700/pcreat + BW/4 + urea/2 – 100/height (m)2
Female: 25 + 6700/pcreat + BW/4 + urea/2 – 100/height (m)2

Nankivell 2 (mL/min)
Male: 71.4 + (5,520/pcreat) + (0.27 * BW) – (age/2) – (0.29 * height)
Female: 50.4 + (5,520/pcreat) + (0.27 * BW) – (age/2) – (0.29 * height)

Salazar and Corcoran (mL/min)
Male: {(137 - age) * [(0.285 * BW) + (12.1 * Ht * Ht)]}/(51 * screat)
Female: {(146 - age) * [(0.287 * BW) + (9.74 * Ht * Ht)]}/(60 * screat)

Walser (mL/min/3 m²)
Male: 7,570/pcreat – (0.103 * age) + (0.096 * BW) – 6.66
Female: 6,050/pcreat – (0.08 * age) + (0.08 * BW) – 4.81

Agarwal and Nicar (mL/min/1.73 m²)
Male: [(163.95 – age) * BW * 1.057]/pcreat
Female: [(190.43 – age) * BW * 0.707]/pcreat

Gates (mL/min/1.73 m²)
Male: [89.4 + (55-age) * (0.005 * 89.4)]/screat 1.2
Female: [60 + (56-age) * (0.005 * 60)]/screat 1.2

Jelliffe 1 (mL/min/1.73 m²)
Male: (100/screat) - 12
Female: (80/screat) - 7

Jelliffe 2 (mL/min/1.73 m²)
Male: {98 - [16 * [(age - 20)/20]]}/ screat
Female: correction factor 0.85

Simplified MDRD (Levey et al) (mL/min/1.73 m²)
Male: 186 * screat - 1.154 * age - 0.203
Female: correction factor 0.742

Nguyen (mL/min/1.73 m²)
218.1 – 0.916 * age – 0.635 * pcreat

Toto (mL/min/1.73 m²)
Male: -0.30 * (age – 52) + (9,282/pcreat) + BW – 86
Female: -0.29 * (age – 52) + (7,780/pcreat) – 0.77 * (BMI – 30)

Rule (mL/min/1.73 m²)
Male: exp (1.911 + 5249/screat – 2114/screat2 – 0.00686 * age)
Female: exp (1.911 + 5249/screat – 2114/screat2 – 0.00686 * age – 0.205)

Body mass index is associated with altered renal hemodynamics in non-obese healthy subjects

Chapter 3

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Abstract

Background. Weight excess is associated with increased renal risk. Data in overt obesity suggest a role for altered renal hemodynamics. Whether body mass index (BMI) is also relevant to renal function in non-obese subjects is unknown.

Methods and results. We studied the relation between BMI and renal hemodynamics in 102 healthy, non-obese (BMI<30 kg/m²) subjects (59 males, 43 females, mean age 39 (18-69) years) in a post-hoc analysis of subjects evaluated as prospective kidney donors or as healthy volunteers in renal hemodynamic studies.
Mean (±SD) BMI was 24.0±2.8 kg/m², MAP 93±11 mmHg, glomerular filtration rate (GFR, iothalamate clearance) 111±19 ml/min/1.73m², effective renal plasma flow (ERPF, hippuran clearance) 458±108 ml/min/1.73m², FF (GFR/ERPF) 0.25±0.04. On univariate analysis, BMI correlated negatively with ERPF/1.73m² body surface area (BSA) ($r=-0.46$; $p<0.001$), GFR/1.73m² BSA ($r=-0.24$, $p=0.013$) and positively with FF ($r=0.45$, $p<0.001$), and age ($r=0.47$, $p<0.001$). On multivariate analysis both BMI and age were independent predictors of ERPF/1.73m² BSA (negative) and FF (positive, all $p<0.05$). Age was the only predictor of GFR/1.73m² BSA (negative). Analyzed for renal function indexed for height (h), BMI correlated negatively with ERPF/h ($r=-0.274$, $p=0.005$), but not with GFR/h ($r=0.13$, $p=0.899$). On multivariate analysis both BMI (positive) and age (negative) were independent predictors for GFR/h (both $p<0.001$). Age was the only predictor for ERPF/h (negative). Predictors for FF (BMI and age, both positive) were by definition unaltered.

Conclusions. The impact of BMI on renal function is not limited to overt obesity, as in subjects with BMI<30 kg/m² a higher BMI is associated with a higher FF, that is, a higher GFR relative to ERPF. This suggests an altered afferent/efferent balance and higher glomerular pressure (i.e., a potentially unfavorable renal hemodynamic profile) that may confer enhanced renal susceptibility when other factors, such as hypertension or diabetes are superimposed.

Introduction

Obesity is increasingly recognized as a risk factor for renal function loss in several conditions such as after unilateral nephrectomy (1), in IgA nephritis (2) and in renal transplant recipients (3-6), although not all studies are equivocal. The mechanism underlying the increased renal risk of obesity is only partly characterized. It may be related to the concomitant cardiovascular and renal risk factors associated with obesity, such as hypertension and diabetes mellitus (7-12). In line with this assumption, altered renal hemodynamics have been implicated, as hyperfiltration - attributed to impaired glucose tolerance - is reported in obese subjects (7;9;13). However, experimental and clinical studies suggested an increased renal risk in obese subjects without overt comorbidity as well (1;14-16).

Weight excess is a continuous trait, and on a population basis, moderate weight excess has a much higher prevalence than overt obesity [body mass index (BMI)>30 kg/m^2]. Data in renal transplant recipients suggest that the impact of BMI on long-term renal risk is not limited to subjects with overt obesity (5), but the relationship between BMI and renal hemodynamics in subjects in the non-obese range has not been well characterized. Therefore, in the present study we investigated the relationship between BMI and renal hemodynamics in non-obese subjects, in a post-hoc analysis of data obtained in healthy subjects evaluated as prospective kidney donors or as healthy volunteers in renal hemodynamic studies.

Methods

Patients

The study group consisted of 102 healthy non-obese subjects [59 males, 43 females, mean age 39 (18-69) years] in whom renal hemodynamic measurements had been performed in our department. The subjects were either healthy subjects [n=61, male/female ratio 27/34, mean age 47 (21-69) years] screened for kidney donation or healthy subjects [n=41, male/female ratio 32/9, mean age 24 (18-46) years] previously studied in experimental protocols including renal hemodynamic measurements as reported previously [(17;18) and unpublished data]. The healthy volunteers were studied during a standardized liberal (200 mmol Na^+/day) sodium intake and prospective kidney

donors on an unrestricted sodium intake. Exclusion criteria for the present analysis were: hypertension (defined as repeated seated blood pressure>140/90 mmHg), diabetes mellitus (defined as fasting blood glucose>6.7 mmol/L and/or 2-hour postglucose concentration>11.1 mmol/L) and obesity (defined as BMI>30 kg/m^2). Prospective kidney donors declared unfit, for whatever reason, to donate a kidney were excluded as well.

Renal hemodynamic measurements

Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured by constant infusion of radiolabelled tracers, ^{125}I-iothalamate and ^{131}I-hippurate, respectively, the subjects being in a quiet room, in the semi-supine position. After drawing a blank blood sample, a priming solution containing 0.04 mL/kg body weight of the infusion solution (0.04 MBq of ^{125}I-iothalamate and 0.03 MBq of ^{131}I-hippurate) plus an extra of 0.06 MBq of ^{125}I-iothalamate was given at 08.00 hours, followed by infusion at 12 mL/h. In order to attain stable plasma concentrations of both tracers, a 2-h stabilization period followed, after which baseline measurements started at 10.00 hours. The clearances were calculated as (UxV)/P and (IxV)/P, respectively. UxV represents the urinary excretion of the tracer, IxV represents the infusion rate of the tracer and P represents the tracer value in plasma at the end of each clearance period. This method corrects for incomplete bladder emptying and dead space, by multiplying the urinary clearance of ^{125}I-iothalamate with the ratio of the plasma and urinary clearance of ^{131}I-hippurate (19;20). The filtration fraction (FF) was calculated as the ratio of GFR and ERPF and expressed as percentage. Renal vascular resistance (RVR) was calculated as mean arterial pressure (MAP) divided by ERPF. Blood pressure was measured noninvasively during the renal function measurements by sphygmomanometer. MAP was calculated as diastolic pressure plus one third of pulse pressure. Fat-free mass was estimated as described by Garrow (21) and Salazar (22) as: [weight x (1-A)] + [B x height^2], with A being 0.715 and 0.713, and B being 12.1 and 9.74 for males and females, respectively. Fat mass was calculated as total body weight minus fat-free mass.

Data analysis

To comply with common practice in the literature, data on renal hemodynamic parameters were indexed per 1.73m^2 body surface area (BSA). However, BSA as such is correlated with BMI. As this could induce bias when analyzing for the relationship

between renal parameters/1.73m^2 and BMI, we also indexed the renal hemodynamic parameters for height (14;23). Data are given for both separately.

Data are presented as mean±standard deviation. Associations were analyzed by univariate regression analysis (Pearson). In addition, multilinear regression analysis was applied with BMI, age and MAP as independent variables entered into the regression equation and renal hemodynamic parameters (GFR, ERPF, FF and RVR, respectively) as dependent variables. Finally, to test whether the relationship between BMI and renal hemodynamic parameters were biased by gender differences, or by selection bias due to differences in recruitment source (i.e., healthy volunteer or prospective kidney donor), we also analyzed our data by general linear modeling, including gender and recruitment source as fixed factors in the analysis.

Statistical computations were performed using SPSS, version 10.0 software (SPSS Inc., Chicago, IL, USA). A p-value less than 0.05 was considered statistically significant.

Results

Patient characteristics are presented in Table 1. All subjects had normal renal function. Thirty-eight subjects were overweight, defined as a BMI>25 kg/m^2. BMI was higher in older patients, as apparent from a positive correlation between age and BMI ($r=0.47$, $p<0.001$).

Figure 1 shows the univariate correlations between BMI and renal hemodynamics indexed for BSA (left panels) and height (right panels), respectively. BMI correlated negatively with the BSA-indexed values of ERPF ($r=-0.46$, $p<0.001$) and GFR ($r=-0.24$, $p=0.013$) and positively with FF ($r=0.45$, $p<0.001$, Fig. 2) and RVR ($r=0.54$, $p<0.001$) (data not shown). Univariate analysis for height-indexed renal hemodynamics showed that BMI correlated negatively with ERPF/h ($r=-0.274$, $p=0.005$), but not with GFR/h ($r=0.13$, $p=0.89$). The correlation with FF was similar, by definition. In accordance with the correlation between BMI and FF, fat mass also correlated positively with FF ($r=0.45$, $p<0.001$, Fig. 3). Fat-free mass correlated positively with uncorrected GFR ($r=0.48$, $p<0.001$) – but not with BSA-corrected or height-corrected GFR. No correlation was present between fat-free mass and BMI ($r=0.01$, NS).

Data on multivariate analysis are given in Table 2. As to the BSA-indexed renal parameters, both BMI and age independently predicted ERPF (negatively), FF (positively) and RVR (positively). Age was the only predictor of GFR (negative). MAP

Table 1 Population characteristics (n=102)

Male/female	59/43
Age (years)	39±14
Weight (kg)	75±11
Fat-free mass (kg)	57±9
Fat mass (kg)	19±6
Length (m)	1.77±0.10
BMI (kg/m²)	24.0±2.8
MAP (mmHg)	93±11
GFR/BSA (mL/min/1.73 m²)	111±19
ERPF/BSA (mL/min/1.73 m²)	458±108
FF	0.25±0.04
RVR/BSA (mmHg*1.73/mL/min)	0.22±0.06
GFR/height (mL/min/m)	69±12
ERPF/height (mL/min/m)	286±67
RVR/height (mmHg*m/mL/min)	0.35±0.10

Abbreviations are: BMI, body mass index:; MAP, mean arterial pressure; GFR, glomerular filtration rate; BSA, body surface area, ERPF, effective renal plasma flow; RVR, renal vascular resistance; FF, filtration fraction. Data are mean ± SE.

Table 2 Multivariate data on determinants of renal hemodynamics, indexed for BSA

	GFR (r^2=0.27)		ERPF (r^2=0.51)		FF (r^2=0.30)		RVR (r^2=0.70)	
	ß	P	ß	P	ß	P	ß	P
BMI	-0.012	0.905	-0.174	0.033	0.267	0.007	0.161	0.013
MAP	0.069	0.459	0.058	0.447	0.021	0.816	0.374	<0.001
Age	-0.553	<0.001	-0.649	<0.001	0.382	<0.001	0.532	<0.001

See Table 1 for abbreviations. BMI, MAP and age are entered in the model as independent variables, for GFR, ERPF, FF and RVR as dependent variables. R-square for the respective models for GFR, ERPF, FF and RVR is given in the upper line. Beta-values (standard coefficient b) and P-values are given for each independent variable separately.

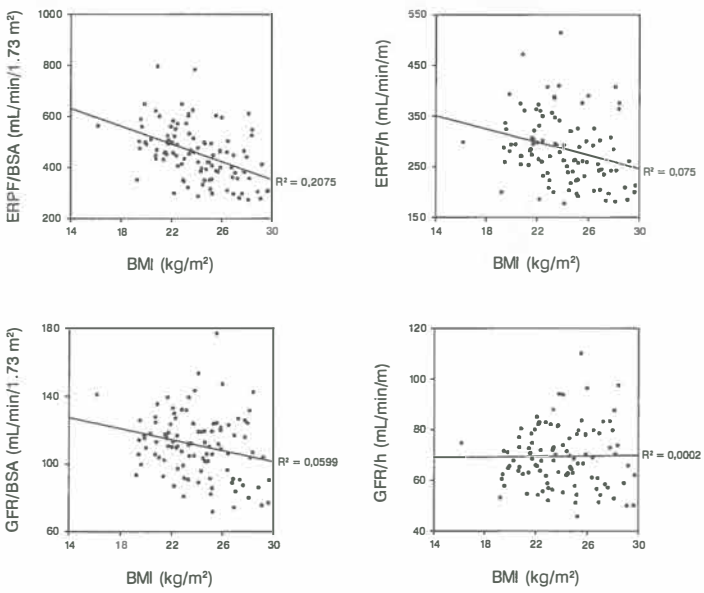
was not a predictor of renal hemodynamics. Multivariate data for the height-indexed renal parameters are given in Table 3. In this analysis age was the only predictor for ERPF and RVR (for both negative). Both BMI (positive) and age (negative) were

Table 3 Multivariate data on determinants of renal hemodynamics, indexed for height

	GFR (r^2=0.31)		ERPF (r^2=0.48)		FF (r^2=0.30)		RVR (r^2=0.68)	
	ß	P	ß	P	ß	P	ß	P
BMI	0.292	0.003	0.049	0.558	0.267	0.007	-0.009	0.893
MAP	0.073	0.422	0.060	0.449	0.021	0.816	0.399	<0.001
Age	-0.656	<0.001	-0.740	<0.001	0.382	<0.001	0.608	<0.001

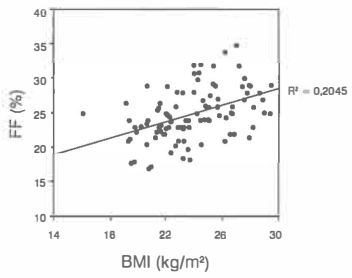
See Table 1 for abbreviations. BMI, MAP and age are entered in the model as independent variables, for GFR, ERPF, FF and RVR as dependent variables. R-square for the respective models for GFR, ERPF, FF and RVR is given in the upper line. Beta-values (standard coefficient b) and P-values are given for each independent variable separately.

Figure 1 Univariate correlations between BMI and renal hemodynamics indexed for BSA and height



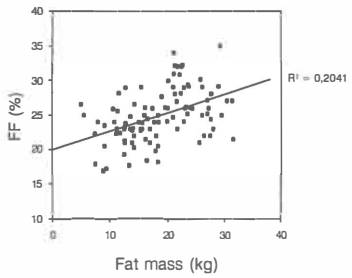
Scatterplots showing the univariate correlation between body mass index (BMI) and effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) indexed for body surface area (BSA)(left panels) as well as ERPF and GFR indexed for height (h)(right panels).

Figure 2 Univariate correlation between BMI and FF



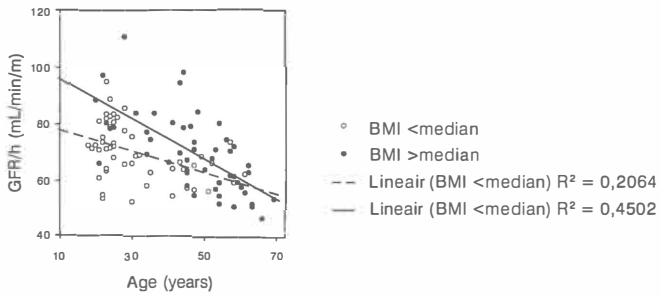
Scatterplot showing the univariate correlation between body mass index (BMI) and filtration fraction (FF).

Figure 3 Univariate correlation between fat mass and FF



Scatterplot showing the univariate correlation between fat mass and filtration fraction (FF).

Figure 4 Multivariate relationship between GFR/h and age with a break-up for BMI below or above the median



Multivariate relationship between glomerular filtration rate (GFR) indexed for height, age and body mass index (BMI). The impact of BMI is visualized by presenting the data-points according to a breakup for BMI below or above the median BMI of this population (median BMI: 23.8 kg/m²) - demonstrating a steeper slope between GFR/h and age for subjects with BMI above the median.

independent predictors for GFR/h as illustrated in figure 4. Predictors for FF (BMI and age, both positive) were by definition similar to those for the BSA-indexed values. To test whether gender or recruitment source affected the relationship between BMI and

renal hemodynamics, general linear modeling was performed with gender, and recruitment source included as factors in the analysis. Whereas this confirmed the significant impact of BMI (r^2 of the model predicting FF: 0.370, $p<0.001$) no significant effect of gender or recruitment source could be detected.

Discussion

In this study we found that a higher BMI is associated with a higher FF in healthy non-obese subjects, suggesting an effect of BMI on afferent/efferent vasomotor balance. Thus, the unfavorable effects of excess weight on renal hemodynamics are not limited to overt obesity.

To compare renal hemodynamics between different individuals with different body size, renal function data are usually indexed for BSA. However, this approach is challenged by studies showing that renal function correlates with height rather than BSA in obese subjects (14;23). For our purpose, moreover, it is relevant to realize that weight gain in a subject of a given body size results in a rise in BSA as well as BMI. Thus, BMI and BSA are strongly correlated. Obviously, this will bias any analysis of the relationship between BSA-indexed renal parameters and BMI towards a negative association. Therefore, we also performed our analysis on height-indexed renal function data. When indexed for BSA, both GFR and ERPF were negatively correlated to BMI, but for GFR this association was annihilated by indexing for height. Our finding, however, that FF is higher in subjects with a higher BMI is not dependent on the way renal function is indexed, and thus stands out as a robust finding not affected by assumptions on the validity of indexing.

Aging has been shown to be associated with a decline in renal function in healthy subjects (24), although comorbidity has been argued to be more important (25). In our study population a higher age was associated with a higher BMI. Thus, the association between BMI and renal hemodynamics observed here might be an age-related artifact. Therefore, we performed multivariate analysis - including age as well as BMI. This revealed that age was indeed the best predictor of renal hemodynamics, irrespective of how renal function was indexed, with lower GFR and ERPF, and higher FF in older patients. Nevertheless, BMI remained an independent positive predictor for FF.

The independent predictive value of age and BMI for GFR/height could suggest that the alleged age-related decline in renal function will be more readily apparent in subjects with a higher BMI. However, our cross-sectional data set does not allow support for such a conclusion, and longitudinal data would be needed to that purpose. Moreover, in our cross-sectional data set the steeper slope between age and GFR/height in the subjects with higher BMI was due to a higher GFR in younger subjects rather than to a lower GFR in the older subjects.

So far, no other studies reported on the impact of BMI on renal hemodynamics in subjects without overt obesity. Most studies on BMI compare lean and (morbidly) obese subjects with obesity defined according to varying cut-off levels. Our observation of a linear relationship between FF and BMI without an apparent cut-off or threshold justifies our approach of analyzing BMI as a continuous trait. The cut-off level of 30 kg/m^2 that we used to exclude overt obesity is in accordance with the National Health and Nutrition Examination Survey (26).

Most studies report that GFR is elevated in obesity. Ribstein et al (9) found that height-indexed GFR was approximately 10% higher in 20 obese normotensive subjects (mean BMI of 33.2) than in lean subjects (mean BMI of 22.4). Chagnac et al (27) reported elevated GFR (not indexed) in severe obesity (BMI>38). An older study on the relationship between body composition and renal function in obesity reported a positive correlation between creatinine clearance and fat-free body mass; as fat-free body mass was elevated in obese subjects this accounted for a higher creatinine clearance in morbid obesity (22). The higher GFR in obesity in those studies is in line with the positive predictive value of BMI for GFR in our multivariate analysis. Anastasio et al (14), however, reported no difference in height-indexed GFR between severely overweight (mean BMI of 46.8) normotensive men and non-obese (BMI of 25.6) control subjects.

Data on ERPF are somewhat more variable between studies. Anastasio et al reported a normal height-indexed ERPF in normotensive obese subjects (14). Other studies, however, found an elevated (height-indexed) ERPF in normotensive as well as hypertensive obese subjects (10). Porter et al found a higher renal perfusion (per kidney volume) in mildly obese, normotensive subjects (15) during severe sodium restriction, but not during liberal sodium intake. Scaglione et al (8), by contrast, reported a lower

(non-indexed) ERPF in normotensive subjects with central obesity. Finally, Schmieder et al (23) reported that height-indexed ERPF was not affected by obesity in a mixed population of hypertensive and normotensive subjects - whereas BSA-indexed ERPF was lower in obese subjects. The absence of impact of BMI on height-indexed ERPF, as well as the negative predictive value of age for ERPF in the latter study, is well in line with our multivariate data.

Differences in indexing may explain some of the above discrepancies, but data on the relationship between FF and BMI are not uniform either, indicating that the discrepancies cannot fully be attributed to differences in indexing. Some authors, in line with our data, report an elevated FF in obesity (27). Ribstein et al, however, found a higher FF in obesity in hypertensive, but not in normotensive subjects (9), suggesting interaction between obesity and hypertension. This is in line with data from Scaglione et al (8) who found an elevated FF in (central) obesity only in hypertensive, but not in normotensive subjects with central or peripheral obesity. The discrepancies suggest impact of comorbidity, such as hypertension (8;9) and insulin resistance (27), but differences in severity of obesity, age, or sodium intake may also have affected the impact of obesity on FF.

Several limitations of our study should be considered. First, possible selection bias. We included only healthy subjects, but our population was not homogeneous as to recruitment source, with prospective kidney donors being older, and with over-representation of younger males among the healthy volunteers. Moreover, being selected for being healthy at middleage (i.e., donors) may select individuals that represent the healthiest part of their age-cohort - which is probably less so for healthy subjects in their twenties. Thus, although we could not detect a significant effect of recruitment source, bias by the heterogeneity in this population cannot be excluded, and it would be relevant to test whether our findings also hold in more homogenous populations. Second, our study was not suitable to identify mechanisms underlying the relationship between BMI and renal hemodynamics - by its post-hoc nature, and by lack of data on possibly relevant factors such as body fat distribution (28), insulin sensitivity, or insulin levels, activity of the sympathetic nervous system (13;29;30) the renin-angiotensin system (RAS) (29;31-33), lipids, and leptin levels. Data in the literature suggest involvement of these factors in renal hemodynamic changes in obesity, and by inference they may also be relevant to the relationship between BMI and renal hemody-

namics in non-obese subjects. Our study did not include formal measurements of body composition. However, as the latter may be relevant as well (22), we estimated fat mass and fat-free mass from anthropomorphic data, and found a significant positive correlation between fat mass and FF. In accordance with data of Salazar et al in a small number of normal and morbidly obese subjects, GFR (uncorrected) correlated positively with fat–free mass. However, in our non-obese population, a higher BMI was not associated with a higher fat-free mass – so the latter does not appear to account for the impact of BMI on renal function that we observed.

A role for insulin resistance in obesity-associated changes in renal function is suggested by the epidemiological association between waist-hip ratio and renal function (28), as well as by the association between obesity-associated increases in GFR (and FF) and the degree of insulin resistance (34). The latter association was blunted by liberal sodium intake (33), which is in line with data from Porter et al, who found an obesity-associated increase in renal perfusion during low sodium only. In our study sodium intake was unrestricted in the majority of the subjects (kidney donors), and standardized at a liberal level in the others. Thus, in our study sodium status, if anything, can be expected to have blunted the relationship between BMI and renal hemodynamics. The impact of sodium intake was suggested to imply a role for the RAS (15), supported by the finding that the renal hemodynamic response to RAS-blockade is proportional to BMI in type II diabetes (35). The mechanism of the link between insulin resistance and renal hemodynamic alterations in obesity has not been elucidated yet. Hyperinsulinemia might be involved, but experimental hyperinsulinemia does not lead to elevated FF, neither in acute nor in chronic experiments (12;36;37), which is at variance with this assumption. Recent data suggest that leptin may be relevant. Serum leptin levels correlate strongly with BMI (38), and leptin stimulates sympathetic nervous activity and reactive oxygen species (39). However, so far, in clinical studies, leptin levels could not be identified as a renal risk factor (40;41).

Animal data on the glomerular microcirculation in obesity indicate changes resembling those after renal ablation, with glomerular hypertension and hyperfiltration. In obese Zucker rats, a genetic model of obesity, GFR was either normal (42;43) elevated (44;45), with either normal (45) or elevated glomerular capillary pressure (43). In this model elevated GFR appears to precede glomerulosclerosis, without, however, being a prerequisite for renal structural damage (42;45). An impaired myogenic afferent

vasoconstriction may be involved in the altered glomerular hemodynamics (46). Food restriction reduces the elevated GFR (40), demonstrating the contribution of a functional component, alongside structural abnormalities. However, the mechanisms of the renal changes in genetically obese models appear to be different from those in man, for instance, regarding the role of the renin-angiotensin system and the sympathetic nervous system (29;43). Obesity induced by over-feeding in dogs and rabbits (47) may more closely mimic the human condition (29). In dogs feeding-induced obesity leads to a considerably elevated GFR and renal plasma flow already after a few weeks, coinciding with structural changes such as mesangial matrix expansion and cell proliferation (7;29), likely precursors of glomerulosclerosis. The elevated GFR has been hypothesized to render the kidney susceptible to progressive glomerulosclerosis, especially when hyperlipidemia, hyperglycemia, or hypertension are simultaneously present. Whether the mechanisms observed in experimental obesity-associated renal damage also apply to our observations on BMI and renal hemodynamics in non-obese subjects, however, remains to be investigated.

What is the clinical impact of our findings? It is well established that the overall health risks of excess weight are not limited to overt obesity (48). As to renal risk, data in renal transplant recipients showed that the renal risk of excess weight is not limited to overt obesity either (5). In line with this, our data indicate that even moderate overweight is associated with an unfavorable renal hemodynamic pattern, i.e., an elevated FF. This may render the kidney susceptible to damage by other renal risk factors, such as hypertension - as supported by the data of Ribstein et al (9). As moderate overweight has a much higher prevalence than overt obesity, the population-attributable risk of overweight for renal damage therefore deserves proper consideration.

Conclusion

The impact of BMI on renal hemodynamics is not limited to overt obesity, as also in subjects with BMI<30 kg/m² a higher BMI is associated with higher GFR relative to ERPF, suggesting altered afferent/efferent balance and a higher glomerular pressure. This potentially unfavorable renal hemodynamic profile may result in enhanced renal susceptibility when other factors, such as hypertension are superimposed. Prospective studies on the impact of overweight on renal risk are needed to confirm these findings.

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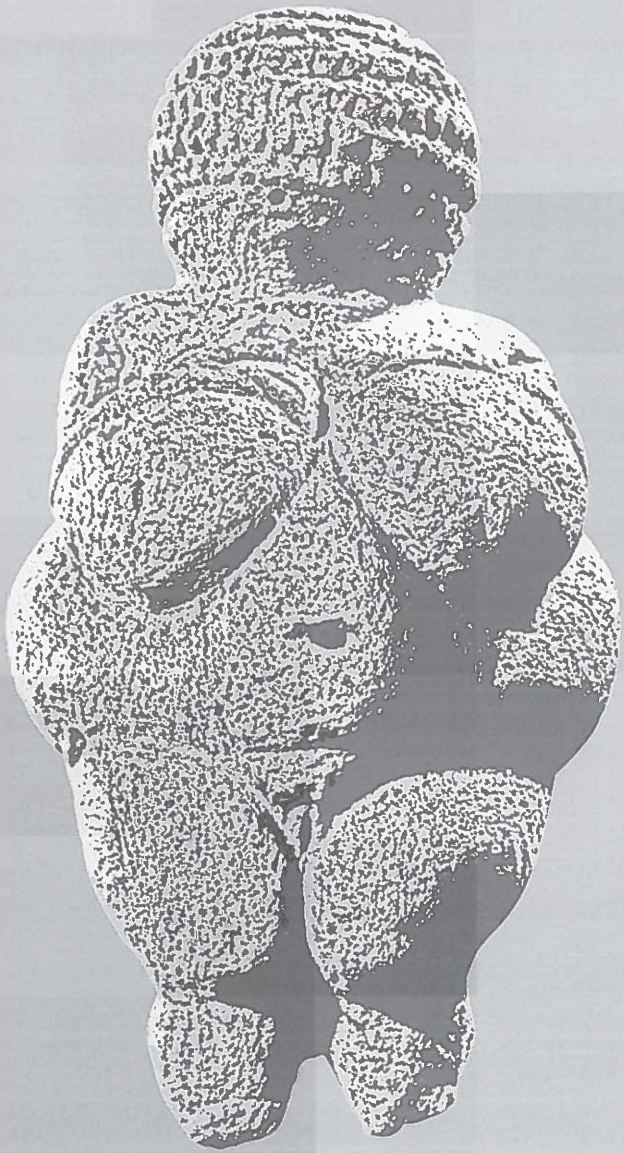

Body mass index and glomerular hyperfiltration in renal transplant recipients:

cross-sectional analysis and long-term impact

Chapter 4

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Abstract

Background. Obesity is a risk factor for renal graft loss. Higher body mass index (BMI) in native kidneys is associated with glomerular hyperfiltration. Whether higher BMI in renal transplants is associated with hyperfiltration is unknown. We investigated the impact of BMI on renal hemodynamics 1 year post-transplant.

Methods and results. We analyzed glomerular filtration rate (GFR, ^{125}I-iothalamate) and effective renal plasma flow (ERPF, ^{131}I-hippurate) in 838 kidney transplants. Data were analyzed for all patients and for the subpopulation without diabetes. Long-term impact of BMI and renal hemodynamics were explored by Cox-regression. With higher BMI GFR and filtration fraction (FF) increased significantly. Multivariate analysis supported impact of BMI on GFR (adjusted r^2 of the model 0.275) and FF (adjusted r^2 of the model 0.158). This association was not explained by diabetes mellitus. On Cox-regression analysis, lower GFR and higher FF were independent determinants of overall graft loss and graft loss by patient mortality. Lower GFR and higher BMI were determinants of death-censored graft loss, with borderline contribution of higher FF.

Conclusions. In renal transplants higher BMI is independently associated with higher GFR and FF one year post-transplant, suggesting glomerular hyperfiltration with altered afferent-efferent balance. Mechanisms underlying the long-term prognostic impact of hyperfiltration deserve further exploration.

Introduction

Obesity is common after renal transplantation. Several studies showed that obesity is a risk factor for impaired renal graft function (1) and graft loss (2-5). In native kidneys obesity is a risk factor for renal function loss as well (6;7). Several mechanisms may be involved in this association. First, obesity is often associated with other renal risk factors, such as hypertension and diabetes mellitus, but independent effects of obesity are also likely. In particular, renal hemodynamic factors have been suggested to play a role, as obesity and even mild overweight are associated with glomerular hyperfiltration, apparent from elevated glomerular filtration rate (GFR) and/or filtration fraction (FF), even when blood pressure and glucose tolerance are normal (8;9).

In renal transplant recipients the mechanisms of the increased renal risk are incompletely characterized, but it has been suggested that hypertension, diabetes and vascular disease may be involved. Whether in renal transplants body mass index (BMI) affects renal hemodynamics is unknown (10). In renal transplants multiple factors, such as cyclosporin use, the single kidney state, and presence of intrinsic renal damage all may affect renal hemodynamics, precluding extrapolation from data in native kidneys to the transplant population. In the present study we therefore investigated whether BMI was a determinant of renal hemodynamics in renal transplant recipients. We studied data obtained at routine evaluation one year after transplantation from 838 consecutive patients transplanted between 1984 and 2002 in our center in a cross-sectional analysis. This analysis showed BMI to be an independent determinant of renal hemodynamics. In an exploratory analysis, subsequently, we tested the long-term prognostic impact of BMI and renal hemodynamics, respectively, on graft survival.

Methods

Patients

The study group consisted of 838 renal transplant recipients, 486 males and 352 females, transplanted between 1984 and 2002, with follow-up data being included until January 2004 (mean age at transplantation 45±13 years) in whom renal hemodynamic measurements had been routinely performed 1 year after transplantation. Of these patients 760 had received a transplant from a deceased donor and 78 a transplant from

a living donor. Mean donor age was 39±16 years, with 472 males and 366 females. Obesity was defined as a BMI>30 kg/m^2. BMI of the recipient was not considered in allocation of donor organs from male or large donors. Diabetes mellitus was found in 135 patients (defined as having at least two values of non-fasting serum glucose>11.1 mmol/L and/or use of glucose lowering medication).

Triple immunosuppressive treatment consisted of cyclosporin A (CsA), azathioprine and steroids. Following the introduction of mycophenolate mofetil (MMF) in May 1997 patients were treated with CsA, MMF and steroids. CsA was started early postoperatively, and doses were adjusted to trough levels of 200-250 ng/ml for the first 3 months. Thereafter doses were slowly tapered to trough levels of 150-200 ng/mL during follow-up. Prednisolone dose of 20 mg/day was tapered over 8 weeks to a maintenance dose of 10 mg/day. MMF was given in a stable dose of 1 g twice daily, starting at day one.

Antihypertensive treatment was given in 605 patients, of whom 83 received RAAS-blockade (ACE inhibitor or angiotensin receptor blocker (ARB)). RAAS-blocker use was equally distributed among the obese and non-obese patients (11.1% versus 9.7%, ns).

Methods

Renal hemodynamic measurements

Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured by constant infusion of ^{125}I-iothalamate and ^{131}I-hippurate, as described by Donker et al (11) and Apperloo et al (12). During the measurements the subjects were in a quiet room in the semi-supine position. After drawing a blank blood sample, a priming solution containing 0.04 mL/kg body weight of the infusion solution (0.04 MBq of ^{125}I-iothalamate and 0.03 MBq of ^{131}I-hippurate) plus an extra of 0.06 MBq of ^{125}I-iothalamate was given at 08.00 a.m., followed by continuous infusion at 12 mL/h. In order to attain stable plasma concentrations of both tracers, a 2 h stabilization period followed, after which baseline measurements started at 10.00 a.m. The clearance was calculated as (UxV)/P and (IxV)/P, respectively. UxV represents the urinary excretion of the tracer, IxV represents the infusion rate of the tracer and P represents the tracer value in plasma at the end of each clearance period. Correction for incomplete bladder emptying and dead space was performed by multiplying the urinary clearance of ^{125}I-iothalamate with

the ratio of the plasma and urinary clearance of ^{131}I-hippurate. As the association between BMI and body surface area induces bias in BSA-normalized data, we refrained from BSA-normalization, and data on GFR and ERPF are given in mL/min. In addition we analyzed the data normalized for height. The filtration fraction (FF) was calculated as the ratio of GFR and ERPF, and expressed as a percentage. Mean arterial pressure (MAP) was calculated as diastolic pressure plus one third of the pulse pressure.

Statistical analysis

The impact of BMI on renal hemodynamics at year one was assessed by univariate analysis and by multivariate analysis. For the univariate analysis, a break-up was made by tertiles of BMI, and BMI-groups were compared by ANOVA followed by post-hoc analysis (Tukey test). Multivariate analysis was conducted in the patients without overt diabetes mellitus - by using multilinear regression - and included BMI, MAP, age (recipient and donor), sex (recipient and donor), ischemia times, HLA mismatches, RAAS-blockade and proteinuria as independent variables. GFR, ERPF and FF were included as dependent variables. To explore the impact of renal hemodynamics and BMI at 1 year after transplantation on graft survival, Cox regression analysis was performed for overall graft loss, death censored graft loss, and graft loss by patient mortality as dependent variables.

Statistical computations were performed using SPSS, version 12.0 (SPSS Inc, Chicago, IL, USA). A p-value less than 0.05 was considered statistically significant.

Results

Table 1a shows the patient characteristics for the whole population (n=838) and for the subpopulation without overt diabetes mellitus (n=703). Mean BMI for the whole population was 26±4 kg/m^2, in 108 patients (13%) BMI was higher than 30 kg/m^2. Mean BMI for the subpopulation without diabetes mellitus was 25±4 kg/m^2, with 80 subjects (11%) having a BMI higher than 30 kg/m^2. Table 1b shows the patient characteristics - including the presence of diabetes mellitus - for the whole population, for tertiles of BMI. By definition, BMI was different between the tertiles. Additionally, recipient age, second warm ischemia time and proportion of subjects with diabetes were significantly higher in the higher BMI tertiles.

Table 1a

	Whole population (n=838)	Subpopulation without diabetes mellitus (n=703)
Recipient sex (male/female)	486/352	413/290
Recipient age (years)	45±13 (14-77)	44±13 (14-77)
Recipient BMI (kg/m²)	26±4 (16-47)	25±4 (16-45)
Donor sex (male/female)	472/366	401/302
Donor age (years)	39±16 (0-71)	44±15 (2-71)
GFR (mL/min)	53±18 (7-115)	53±18 (7-115)
ERPF (mL/min)	213±68 (21-496)	213±67 (21-496)
FF (%)	25±5 (8-50)	25±5 (8-50)
MAP (mmHg)	108±12 (73-167)	108±12 (73-147)
WI time 1 (minutes)	1.2±7.3 (0-80)	1.3±7.9 (0-80)
CI time (hours)	22.0±9.2 (0-44)	22.2±9.3 (2-44)
WI time 2 (minutes)	38.1±11.4 (15-83)	37.8±11.2 (15-83)
HLA MM AB	1.2±1.0 (0-4)	1.2±1.0 (0-4)
HLA MM DR	0.3±0.5 (0-2)	0.4±0.5 (0-2)
RAAS-blockade (n)	83	70
Uprot (g/24 h)	0.5±1.1 (0-18.9)	0.5±1.1 (0-18.9)

Table showing patient characteristics, mean±SD (range) for the whole population and the subpopulation without diabetes mellitus.

Univariate data are given in Figure 1, showing mean values of GFR, ERPF, FF and MAP by tertile of BMI. GFR was significantly higher with higher BMI (ANOVA $p<0.001$), with a significant difference between the highest and lowest tertile on post-hoc analysis. The same relationship was found for height-corrected GFR (data not shown). ERPF also increased per tertile, however the differences were not statistically significant. Identical findings were seen for height-corrected ERPF. Consequent to the values of GFR and ERPF, FF was significantly different for the BMI tertiles, with a higher FF at higher values of BMI (ANOVA $p=0.006$), with a significant difference between the highest and lowest tertile on post-hoc testing. BMI had no impact on MAP.

The number of patients on RAAS-blockade (total n=83) was equally distributed over the tertiles. In all tertiles GFR and FF were significantly lower (all $p<0.001$) in patients with RAAS-blockade than in those without, namely 39 mL/min versus 52 mL/min, 45 mL/min versus 55 mL/min and 49 mL/min versus 57 mL/min for GFR, and 21%

Table 1b

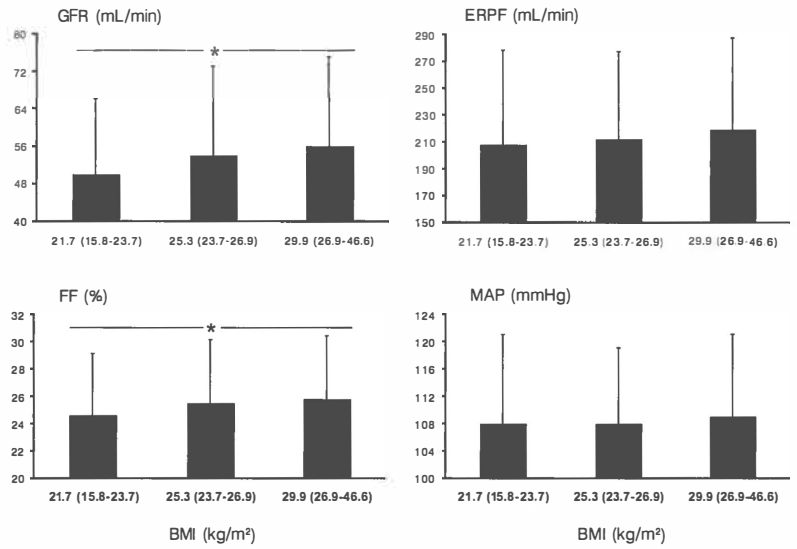
	BMI 1 (n=279)	BMI 2 (n=280)	BMI 3 (n=279)	P
Recipient sex (male/female)	156/123	172/108	158/121	0.357
Recipient age (years)	39±14 (14-77)	47±12 (19-71)	48±13 (17-71)	<0.001
Recipient BMI (kg/m²)	21.7±1.6 (15.8-23.7)	25.3±0.9 (23.7-26.9)	29.9±3.0 (26.9-46.6)	<0.001
Donor sex (male/female)	152/127	158/122	162/117	0.695
Donor age (years)	38±16 (2-69)	39±16 (6-71)	39±15 (1-71)	0.585
WI time 1 (minutes)	1.2±6.9 (0-30)	1.2±6.8 (0-30)	1.3±8.2(0-80)	0.711
CI time (hours)	22.1±9.8 (2-40)	22.1 ±8.7 (2-40)	22.8±9.0 (0-44)	0.651
WI time 2 (minutes)	37.2±10.8 (16-65)	37.2±10.8 (15-70)	40.0±12.5 (15-83)	0.008
HLA MM AB	1.2±1.0 (0-4)	1.2±1.0 (0-4)	1.3±0.9 (0-4)	0.924
HLA MM DR	0.4±0.5 (0-2)	0.4±0.5 (0-2)	0.3±0.5 (0-2)	0.430
RAAS-blockade (n)	27	29	27	0.953
Uprot (g/24 h)	0.5±1.4 (0-18.9)	0.4±0.7 (0-8.2)	0.5±1.1 (0-9.6)	0.381
Diabetes mellitus (n)	31	35	69	<0.001

Table showing patient characteristics, mean±SD (range) for the whole population for tertiles of BMI.

versus 25%, 24% versus 26% and 23% versus 26% for increasing tertiles of BMI for FF. Values for ERPF and MAP were similar in subjects with and without RAAS-blockade.

To analyze whether the univariate data could be confounded by overrepresentation of patients with diabetes mellitus among those with the highest BMI, we conducted the same analysis after exclusion of the overtly diabetic patients. For the 703 non-diabetic patients data are shown in Figure 2 (black bars left of the dashed lines), showing similar findings for GFR (ANOVA p=0.002), ERPF, FF (ANOVA p=0.007) and MAP as for the whole population. For comparison, the values of the subpopulation with diabetes mellitus (n=135) are given as well (gray bars right of the dashed lines). Multivariate analysis (Table 2) was performed in the non-diabetic patients to see whether the effect of BMI on renal hemodynamics was independent of age (of recipient and donor), MAP, ischemia times, HLA mismatches and proteinuria. Indeed, BMI was independently associated with a higher GFR ($p<0.001$, r^2 of the model 0.275), ERPF ($p<0.001$, r^2 of the model 0.197) and FF ($p=0.038$, r^2 of the model 0.158) 1 year after transplantation. Additional determinants for GFR were MAP, donor age, recipient sex, cold ischemia time, RAAS-blockade and proteinuria. Additional determinants for ERPF were MAP,

Figure 1 Univariate analysis

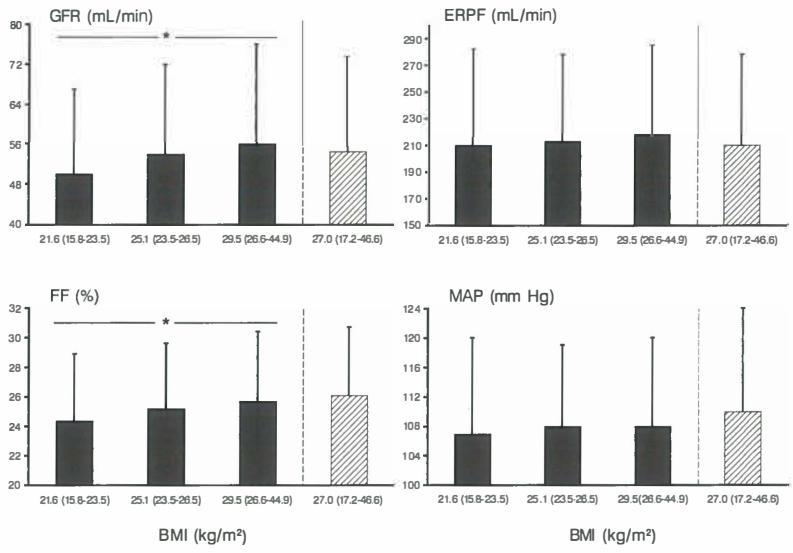


Mean (±SD) values of GFR, ERPF, FF and MAP respectively, by tertile of BMI. Bars show renal hemodynamics at 1 year after transplantation for the whole population (n=838).
* indicates $p<0.05$ (ANOVA)

donor and recipient age, donor and recipient sex, number of HLA-DR mismatches and cold ischemia time. For FF, additional determinants were MAP, recipient and donor age, donor sex, RAAS-blockade and proteinuria. Essentially similar results were obtained when data were analyzed for GFR/height (data not shown).

To test whether the impact of BMI on renal hemodynamics was persistent over time, we also measured renal hemodynamics at 5 years after transplantation in the same patients, and analyzed by BMI tertile of year 1. At that time 112 grafts had been lost - 47 due to graft failure, and 65 as a result of patient mortality. Of the remaining 726 patients, data on renal hemodynamics at year 5 were available in 545 patients in whom data had been obtained at year 1 as well. At year 5 numerical differences were present by increasing BMI tertile for GFR (51±18 mL/min versus 53±21 mL/min versus 55±21 mL/min) and FF (23±5% versus 24±5% versus 24±5%), that did however not reach statistical significance. In a paired test between year 1 and 5, in the lower tertiles

Figure 2 Univariate analysis



Mean (±SD) of GFR, ERPF, FF and MAP respectively, by tertile of BMI for the non-diabetic subjects (n=703, black bars left of the dashed lines). For comparison, data on GFR, ERPF, FF and MAP in the diabetic subjects are shown as well (n=135, gray bars right of the dashed lines). * indicates $p<0.05$ (ANOVA)

of BMI GFR remained stable (51±15 mL/min versus 51±18 mL/min and 55±18 mL/min versus 53±21 mL/min for tertile 1 and 2 respectively), with a significantly lower FF at year 5 (25±4% versus 23±5% and 26±4% versus 24±5% for tertile 1 and 2 respectively, both $p<0.001$). For the highest tertile GFR was significantly lower at year 5 (59±18 mL/min versus 55±21 mL/min, $p=0.002$), with a lower FF as well (26±4% versus 24±5%, $p<0.001$). Individual changes in renal hemodynamics between year 1 and 5 were not related to changes in BMI.

Long-term impact of BMI and renal hemodynamics on graft survival

To explore the possible long-term impact of BMI and its renal hemodynamic correlates for graft survival Cox-regression analysis was performed for overall graft loss, death-censored graft loss, and graft loss by patient mortality, respectively. During the follow-up period overall graft loss amounted to 268/838 grafts, death-censored graft

Table 2

	GFR (r^2=0.275)		ERPF (r^2=0.197)		FF (r^2=0.158)	
	ß	P	ß	P	ß	P
BMI	0.183	<0.001	0.137	<0.001	0.078	0.038
MAP	-0.074	0.036	-0.145	<0.001	0.119	0.002
Recipient age	-0.047	0.185	-0.124	0.001	0.133	<0.001
Donor age	-0.404	<0.001	-0.302	<0.001	-0.259	<0.001
Recipient sex (male)	0.137	<0.001	0.135	<0.001	0.048	0.196
Donor sex (male)	0.026	0.450	0.080	0.027	-0.123	0.001
WI time 1	-0.053	0.120	-0.060	0.094	-0.003	0.926
CI time	-0.189	<0.001	-0.177	<0.001	-0.052	0.178
WI time 2	0.010	0.772	0.006	0.870	0.010	0.797
HLA MM AB	-0.043	0.221	-0.011	0.770	-0.059	0.121
HLA MM DR	-0.056	0.125	-0.090	0.020	0.051	0.199
RAAS-blockade	-0.141	<0.001	-0.069	0.059	-0.110	0.003
Uprot	-0.134	<0.001	0.020	0.590	-0.155	<0.001

Table showing multivariate analysis of the determinants of renal hemodynamics in the subjects without diabetes mellitus, n=703.

Table 3

Covariates	Overall graft loss		Death censored graft loss		Graft loss by patient mortality	
	Exp(B)	P	Exp(B)	P	Exp(B)	P
Age	1,033	0,000	0,977	0,007	1,062	0,000
Recipient sex (male)	0,715	0,012	0,543	0,006	0,778	0,106
BMI	1,024	0,197	1,081	0,003	1,002	0,924
MAP	1,008	0,165	1,007	0,434	1,010	0,112
Uprot	1,207	0,000	1,157	0,001	1,241	0,000
GFR	0,969	0,000	0,948	0,000	0,975	0,000
FF	1,031	0,040	1,045	0,053	1,046	0,011
RAAS-blockade	1,038	0,866	1,376	0,311	0,893	0,705

Table showing the long-term impact of body mass index and glomerular hyperfiltration at one year after transplantation; Cox regression analysis model summary.

loss to 100/838 grafts, and graft loss by patient mortality to 168. The summary of the respective Cox-regression models is given in Table 3. It shows that the independent determinants of overall graft loss were a higher age, recipient sex, proteinuria, a lower GFR and a higher FF, whereas blood pressure, BMI and RAAS-blockade were not included in the model. For death-censored graft loss the independent determinants were a younger age, recipient sex, a higher BMI, proteinuria and a lower GFR, whereas a higher FF was of borderline significance. RAAS-blockade and blood pressure were not included in the model. Finally, independent determinants of graft loss by patient mortality were a higher age, proteinuria, a lower GFR and a higher FF, whereas blood pressure and recipient sex were of borderline significance and BMI and RAAS-blockade were not entered into the model. Inclusion of donor age and donor sex into the model did not improve the models, and these covariates did not reach significance (data not shown).

As an increase in BMI after transplantation has been reported to be associated with graft loss, we finally tested whether an increase in BMI of more than 5% predicted graft loss. A comparable Cox regression analysis model was used (covariates: GFR, FF, increase in BMI more than 5%, blood pressure, recipient and donor age, donor sex and RAAS-blockade, and proteinuria). An increase in BMI of more than 5% in the first year after transplantation was observed in 663/838 patients. This increase, however, was not a predictor for graft loss.

Discussion

In this study, we showed that in renal transplant patients a higher BMI is independently associated with a higher GFR and FF, one year after transplantation. On multivariate analysis ERPF was determined by BMI as well. The impact of BMI on renal hemodynamics was not explained by the presence of overt diabetes. On long-term follow-up, a higher FF was associated with the risk for overall graft loss, by an effect on patient mortality and a borderline effect on death-censored graft loss, whereas BMI was associated with death-censored graft loss but not patient mortality.

We recently demonstrated a relationship between BMI and renal hemodynamics in a group of healthy subjects, with a higher GFR and FF in subjects with a higher BMI (9).

In the renal transplant population, however, many factors can influence overall renal hemodynamics and the afferent/efferent balance, such as nephrotoxic agents (eg calcineurin inhibitors), other drugs that affect renal hemodynamics such as RAAS-blockers, viral infections, ischemic reperfusion injuries, acute rejection and the single kidney state. To overcome the potential confounding effects of acute events, we studied the patients one year after transplantation, in a stable condition and not in the immediate post-transplant period, in which the occurrence of these factors is more common. Our present data show that the impact of BMI is apparently sufficiently robust to be discernible despite the various other factors that affect renal hemodynamics in renal transplant recipients.

A high BMI has been shown to be a risk factor for long-term renal graft loss (2-4). The risk conferred by high BMI is assumed to be multifactorial, including diverse factors, such as hypertension, concomitant cardiovascular factors and diabetes mellitus. So far, no data were available on the renal hemodynamic effects of BMI in the adult transplant population. Our data, in particular the association between a higher BMI and a higher filtration fraction suggest that a higher BMI may be associated with a higher filtration pressure, which can be a factor contributing to long-term renal function loss in the graft. Indeed in our study BMI was an independent predictor of death-censored graft loss. This confirms the role of BMI as a renal risk factor in our population, as also supported by the longitudinal decrease in GFR between year 1 and 5 in the highest BMI tertile only. An independent effect of a higher FF on death-censored graft loss was found as well, albeit of borderline statistical signficance. Remarkably, however, a higher FF - along with well-established risk factors such as age, sex, GFR and proteinuria, was an independent predictor for graft loss by patient mortality and overall graft loss.

The prognostic impact of FF for mortality is remarkable and to the best of our knowledge has not been described before. The mechanism underlying this association would be of interest, but our study does not allow the identification of such mechanisms. In non-transplant populations a higher FF was found to be associated with impaired cardiac function, and/or left ventricular hypertrophy (13-15), both risk factors for mortality. Prospective data including cardiac evaluation would be required to see whether underlying cardiac disease is involved in the predictive effect of FF for patient failure. Of note, graft loss by patient mortality considerably outnumbered death-censored graft loss. Accordingly, the power of our study to identify the long-term renal

consequences of a higher FF, as assessed from death-censored graft loss, was reduced by the competing risk for graft failure by patient mortality.

Several other, smaller, studies addressed renal function in association with obesity in renal transplant recipients - however only providing data on GFR or creatinine clearance and without assessment of ERPF and FF (10;16;17). In these studies no hyperfiltration was detected, but it was shown that obesity was associated with worse renal outcomes. An elegant study by Yamamoto et al (18) on paired cadaveric kidneys showed that recipient obesity was not a risk factor for delayed graft function (DGF) or acute rejection and did not lead to a lower 1-year graft survival. However, after a follow-up of 5 years recipient obesity was associated with a significantly decreased graft survival. Thus, the renal risk associated with recipient obesity in renal transplantation is apparently a long-term risk. Finally, one recent study drew attention to the impact of weight gain during the first year after transplantation as a risk factor for graft loss (19). Our data, however, could not confirm this association.

Our study was not designed to unravel the mechanisms underlying the impact of body mass index on renal hemodynamics. The mechanisms may be related to concomitant cardiovascular and renal risk factors associated with obesity, such as diabetes mellitus and hypertension, with RAAS activity (20;21) and/or sympathetic activity (22;23) as relevant pathways. Also in obese, otherwise healthy subjects renal hemodynamics appear to be RAAS dependent (21). Our present data in transplant recipients allow several inferences on the effect of BMI on renal hemodynamics. First, they apparently occur in the single kidney setting, and accordingly, in a presumably denervated kidney. Second, it should be noted that it was recipient BMI that affected hemodynamics in the donor kidney, suggesting that the association between BMI and renal hemodynamics is due to factors exogenous to the kidney, such as circulating factors. It should be noted in this respect, however, that we did not have reliable data on donor BMI - so confounding by effects of donor BMI cannot completely be excluded. Finally, the association between BMI and renal hemodynamics in our study was not explained by presence of overt diabetes, but it should be noted that we cannot rule out an effect of impaired glucose tolerance.

What could be the implications of our findings? Our results support the impact of both BMI and renal hyperfiltration, as apparent from FF, as independent risk factors for graft

loss. Obviously, long-term preservation of graft function requires a multifactorial approach, with control of hypertension, dyslipidemia and glycemic regulation. Our data seem to indicate that in transplant recipients with high BMI renal hemodynamics might provide a target for intervention. In this respect RAAS-blockade should be considered as a possible approach, as the renal hemodynamic profile associated with obesity is ameliorated by ACE inhibition in healthy subjects (21). In our study RAAS-blockade was associated with lower GFR and FF, suggesting that it ameliorates glomerular hyperfiltration in renal transplants. Whereas it could be argued that RAAS-blockade did not affect long-term outcome in our study, obviously our study was not designed or powered to this purpose. As to the specific renal risk (estimated from death-censored graft loss) it should be noted, that BMI exerted an effect that was independent of renal hemodynamics and blood pressure, and that may require specific additional interventions, for instance aimed at correction of weight excess. It would be attractive, furthermore, to investigate whether RAAS-blockade could reduce graft loss by patient mortality. The beneficial effects of RAAS-blockade in conditions characterized by excess neurohumoral activity, such as heart failure, are well-established (24) and it would be reasonable to speculate that the association between elevated FF and patient failure reflects excess neurohumoral activation, related to cardiac factors, weight excess or other. Prospectively controlled studies would be needed to identify the long-term protective effects of RAAS-blockade in renal transplant recipients.

In conclusion, higher BMI induces glomerular hyperfiltration in renal transplant patients. This unfavorable hemodynamic profile is not explained by the presence of overt diabetes mellitus. A higher FF was associated with graft loss, predominantly by patient mortality, whereas BMI was only associated with death-censored graft loss. The mechanisms underlying the prognostic impact of an elevated FF in the transplant population deserve further exploration.

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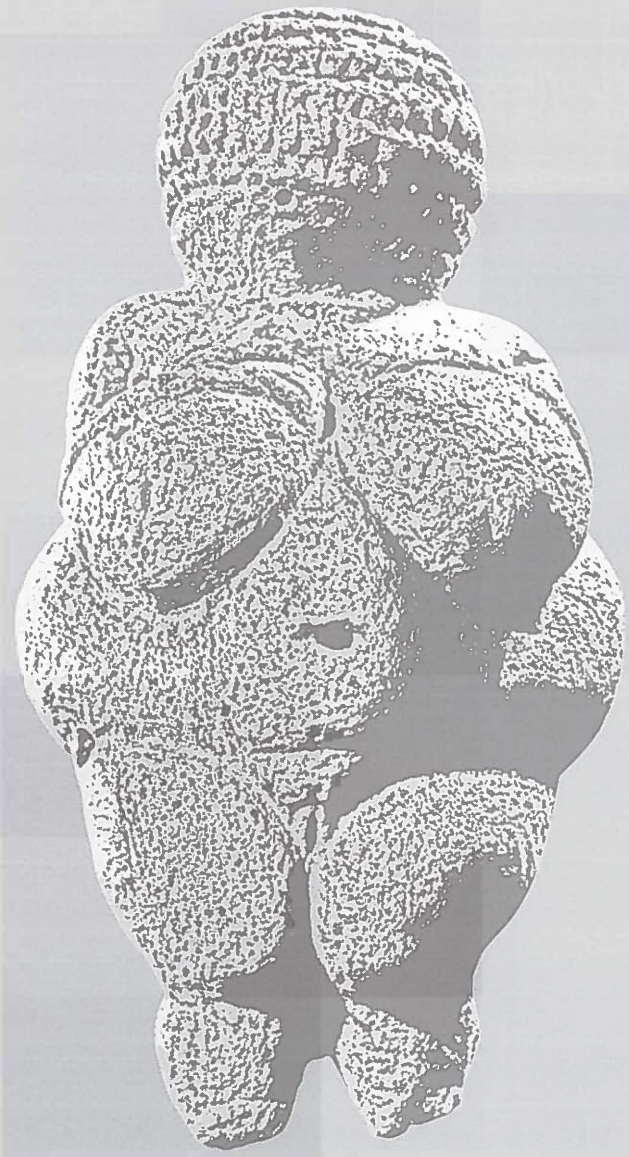

Renal functional reserve after living kidney donation is more reduced in donors with higher body mass index or older age

Chapter 5

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Submitted

Abstract

Background. Renal functional reserve could be relevant for maintenance of renal function after kidney donation. Older age and higher body mass index (BMI) may be associated with reduced reserve capacity (RC). We therefore investigated RC in 178 consecutive living kidney donors (39% male, age 48±11 years, BMI 25.5±4.1). RC was determined as the rise in glomerular filtration rate (GFR; ^{125}I-iothalamate) after constant infusion of low-dose dopamine, 4 months before and 2 months after donor nephrectomy.

Methods and results. Before donor nephrectomy, GFR was 114±20 mL/min, with a reduction to 72±12 mL/min after donor nephrectomy. The dopamine-induced rise in GFR of 11±10% was reduced to 5±7% after donor nephrectomy ($p<0.001$). Before donor nephrectomy, older age and higher BMI did not affect reserve capacity. After donor nephrectomy, the response of GFR to dopamine independently and negatively correlated with older age and higher BMI. Moreover, post-donation reserve capacity was absent in obese donors. Presence of overweight had more impact on loss of RC in younger donors.

Conclusions. Donor nephrectomy unmasked an age- and overweight-induced loss of reserve capacity. Possibly, donors with advanced age and/or overweight address their renal reserve to maintain renal function.

Introduction

The kidney has a substantial functional reserve capacity that is assumed to be relevant for preservation of renal function after loss of functional renal mass, for instance after living kidney donation. Renal reserve capacity can be estimated from the renal hemodynamic response to intravenous administration of low-dose dopamine, an amino-acid solution or an oral protein load (1-3). The resulting increase in glomerular filtration rate (GFR) is considered to be a reflection of renal reserve capacity.

Older age, by loss of nephrons and/or renal arteriosclerosis, has been associated with reduced renal reserve capacity (4-6). In presence of hypertension, obese patients were also reported to have reduced renal reserve capacity, compared to lean hypertensive subjects (7), possibly due to hyperfiltration. However, data are not consistent, which may be due to relatively small study populations and differences in patient selection (8,9). In a large series of 125 prospective living kidney donors (mean age 49±11 years; mean BMI 25±4 kg/m^2), we did not find renal reserve capacity to be reduced in older or more overweight donors during pre-donation screening, presumably because kidney donors represent a healthy subset of the population. However, higher age and higher BMI were independently associated with a larger decrease in renal function early after donation, suggesting impairment in renal adaptive capacity. This had not been detected from the renal hemodynamic responses to dopamine and amino acids prior to donation (10).

Effects of age and overweight on renal risk after living kidney donation is of clinical relevance, as - due to persistent donor shortage - older and/or overweight subjects are increasingly accepted for kidney donation. This implies that the long-term renal risk profile for the current donor population may not be similar to that of the former, healthier, donor population (11).

After kidney donation, renal hemodynamic reserve capacity is decreased (12-14), most likely resulting from a state of renal vasodilatation that occurs in the remaining kidney as part of the compensatory response (12). It is unknown whether renal reserve capacity after kidney donation is affected by risk factors for renal function loss, such as older age and higher body mass index.
Based on the above studies, we hypothesized that the decrease in renal reserve

capacity after kidney donation would be larger in older and in overweight subjects. To test this hypothesis, we analyzed data on renal reserve before and early after donation in 178 living kidney donors and analyzed for the impact of age and BMI.

Methods

Subjects

The study population consisted of 178 consecutive living kidney donors (age 48±11 years, 39% male, mean BMI 25.5±4.1 kg/m^2) who underwent the screening protocol with subsequent donation in the University Medical Center Groningen between 1984 and 2005. All donors were normotensive or with well-regulated blood pressure by maximum of one antihypertensive drug (8 subjects), they did not have a history of diabetes, kidney disease or cardiovascular events. Potential donors with latent diabetes, identified by abnormal oral glucose tolerance test, were excluded from donation. Physical examination did not reveal abnormal findings. In our center, glomerular filtration rate (GFR) and its reserve capacity are routinely measured as part of the living donation protocol. As described below, GFR was measured as the clearance of ^{125}I-iothalamate, first without stimulation, and directly hereafter during stimulation by low-dose dopamine. Measurements were performed 4 months before and 2 months after kidney donation. All donors consented with the use of their clinical data for study purposes.

Renal hemodynamic measurements

GFR was measured by combined constant infusion of radio-labeled tracers ^{125}I-iothalamate and ^{131}I-hippurate, the donors being in a quiet room, in the semi-supine position. After drawing a blank blood sample, a priming solution containing 0.04 mL/kg body weight of the infusion solution (0.04 MBq of ^{125}I-iothalamate and 0.03 MBq of ^{131}I-hippurate) plus an extra of 0.06 MBq of ^{125}I-iothalamate was given at 08.00 hours a.m., followed by infusion at 12 mL/h. In order to attain stable plasma concentrations of both tracers, a 2-hour stabilization period followed, after which baseline measurements started at 10.00 hours a.m. The clearances were calculated as (U*V)/P and (I*V)/P, respectively. U*V represents the urinary excretion of the tracer, I*V represents the infusion rate of the tracer and P represents the tracer value in plasma at the end of each clearance period. This method corrects for incomplete bladder emptying and dead

space, by multiplying the urinary clearance of ^{125}I-iothalamate with the ratio of the plasma and urinary clearance of ^{131}I-hippurate (15).

To obtain reserve capacity, the above-described baseline procedure was extended for 2 hours. During this period, dopamine was infused at a rate of 1.5 μg/kg per minute. GFR during these 2 hours was compared with baseline GFR and expressed as a percentage.

Body mass index (BMI) was calculated as (BODY WEIGHT / LENGTH^2) and divided into classes as follows: normal weight: BMI<25 kg/m^2, overweight: BMI 25-29.9 kg/m^2, obesity: BMI≥30 kg/m^2.

Statistical analysis

Data are presented as mean±standard deviation unless stated otherwise. Associations were analyzed by univariate analysis (Pearson). In addition, multi-linear regression analysis was applied with age and BMI as independent variables entered into the regression equation and renal hemodynamic parameters (proportional rise in GFR) as dependent variables. Influence of donor age on renal function and reserve was assessed by age as a continuous variable as well as by tertiles of age. Differences in reserve capacity between BMI classes were analyzed by analysis of variance (ANOVA) followed by post-hoc analysis (LSD) to account for multiple comparisons. Furthermore, we applied ANOVA and post-hoc analyses to reserve capacity in the different tertiles of age. To account for possible interaction between BMI and age, the interaction term was calculated as BMI*AGE, and analyzed as a continuous variable. Finally, ANOVA and general linear modeling were applied to the combination of BMI and age. Statistical analyses were performed by using SPSS version 14.0 software (SPSS Inc., Chicago, IL, USA). A p-value less than 0.05 was considered statistically significant.

Results

Characteristics

39% of donors were male. Mean donor age was 48±11 years and mean BMI was 25.5±4.1 kg/m^2. The population characteristics are given in Table 1a for break up by BMI class and in Table 1b for break up by tertiles of age. Before kidney donation,

Table 1a

	Normal (n=87)	Overweight (n=70)	Obese (n=21)	p-value (ANOVA)
Before donation				
Age (years)	46±11	49±11	52±8	0.072
Body mass index (kg/m²)	22.4±1.7	27.0±1.4	33.5±3.7	<0.0001
Percentage male donors	34%	47%	33%	NS
GFR baseline (mL/min)	111±15	117±23	119±24	0.070
GFR on dopamine (mL/min)	122±19	129±28	132±27	0.103
Serum creatinine (mg/dL) [1]	0.9±0.1	1.0±0.1	0.9±0.1	0.117
After donation				
GFR baseline (mL/min)	70±11	74±13	74±11	0.103
GFR on dopamine (mL/min)	75±14	77±13	76±12	0.776
Serum creatinine (mg/dL) [2]	1.3±0.2	1.4±0.2	1.3±0.2	0.009

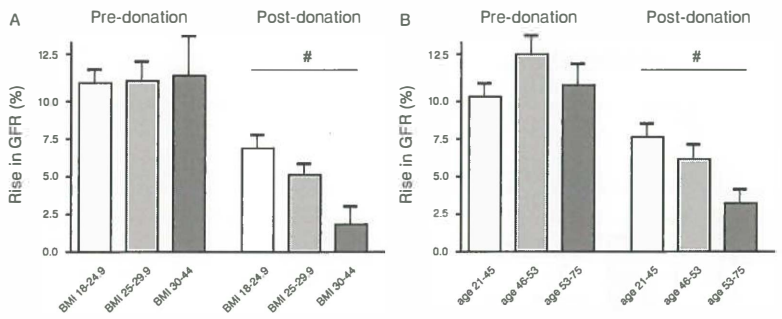
Data are provided as mean±standard deviation; normal weight: BMI<25, overweight: BMI 25-29.9, obese: BMI≥30. ANOVA was used to test the differences between the weight classes. Creatinine in μmol/L: [1] before donation, normal weight 83±11; overweight 86±13; obese 80±11; [2] after donation, normal weight 111±17; overweight 120±19; obese donors 115±20. Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; ANOVA, analysis of variance. Dopamine-stimulated GFR values compared to baseline values: both p<0.001, before as well as after donation (paired t-tests for total group).

Table 1b

	1st tertile (n=87)	2st tertile (n=70)	3st tertile (n=21)	p-value (ANOVA)
Before donation				
Age (years, range)	21-45	46-53	54-75	<0.001
Body mass index (kg/m²)	24.3±4.3	25.8±3.9	26.5±4.0	0.012
Percentage male donors	40%	37%	40%	NS
GFR baseline (mL/min)	123±19	113±19	105±17	<0.001
GFR on dopamine (mL/min)	135±23	127±23	116±22	<0.001
Serum creatinine (mg/dL) [1]	0.9±0.1	0.9±0.1	1.0±0.2	0.863
After donation				
GFR (mL/min)	77±10	72±12	66±10	<0.001
GFR on dopamine (mL/min)	83±11	77±13	68±11	<0.001
Serum creatinine (mg/dL) [2]	1.3±0.2	1.3±0.2	1.3±0.3	0.094

Data are provided as mean±standard deviation unless stated otherwise. ANOVA was used to test the differences between the tertiles. Creatinine in μmol/L: [1] before donation, first tertile 84±9; second tertile 83±11; third tertile 84±15; [2] after donation, first tertile 112±16; second tertile 114±16; third tertile 119±23. Abbreviations: GFR, glomerular filtration rate; ANOVA, analysis of variance.

Figure 1 BMI and age related differences in renal reserve capacity



Renal reserve capacity is expressed as the percentage rise in GFR after infusion of low-dose dopamine. There were no statistically significant differences in pre-donation reserve capacity between the groups of BMI or age (all ANOVA p>0.10). After donation, reserve capacity was more reduced in donors with higher BMI and older age, listed in detail below.

A Post-donation reserve capacity differs between BMI class: p=0.005 (ANOVA). Post-hoc analyses: overweight vs. normal weight p=0.086, overweight vs. obese p=0.046. Obese vs. normal weight p=0.002. Normal weight: n=87; overweight: n=70; obese: n=21.

B Post-donation reserve capacity differs between tertiles of age at donation: p=0.006 (ANOVA). Post-hoc analyses: oldest vs. middle tertile p=0.036. Oldest vs. youngest tertile p=0.002.

Abbreviations; BMI, body mass index; GFR, glomerular filtration rate.

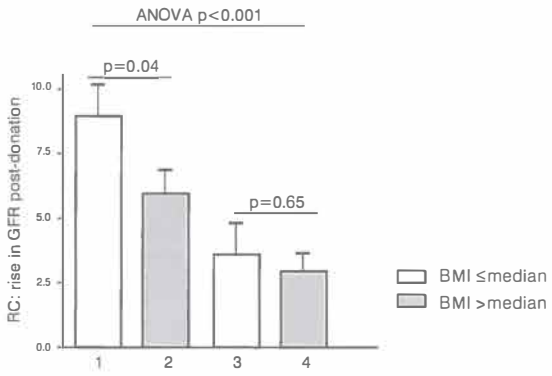
baseline GFR was 114±20 mL/min, with a reduction to 64±7% of pre-donation values after donation (p<0.001). Before donation, infusion of low-dose dopamine significantly increased GFR to 126±24 mL/min, p<0.001 versus baseline. After donation, infusion of low-dose dopamine induced an increase in GFR from 72±12 mL/min to 76±13 mL/min (p<0.001 versus post-donation baseline values).

Pre-donation GFR was highest in obese donors, however, this was merely of borderline statistical significance (ANOVA p=0.07). As anticipated, GFR was significantly lower in the older age groups, before as well as after donation (Table 1).

Influence of BMI or age on renal reserve

Figure 1 shows the percentage change in GFR after stimulation with dopamine before and after donation for each class of BMI (upper panel) as well as for tertiles of donor

Figure 2 Combined effect of BMI and age in differences in the dopamine induced rise in GFR after living kidney donation



Data are expressed as mean±standard error. Four groups of equal size were obtained by dividing first across median age and second across median BMI of either group. Group 1 (reference group): age≤49 and BMI<24.2 (n=44); group 2: age≤49 and BMI≥24.2 (n=45); group 3: age>49 and BMI<25.8 (n=44); group 4: age>48.9 and BMI≥25.8 (n=45). P<0.001 by ANOVA. Compared to reference group 1, there was a statistically significant lower reserve capacity in GFR in donors from group 2 (p=0.04), 3 (p<0.001) and group 4 (p<0.001; all post-hoc analyses). Whereas RC was reduced to a greater extent in younger donors with overweight, in older donors, being normal weight or overweight did not influence the amount of renal reserve reduction (p=0.65 post-hoc).

age (lower panel). The mean rise in GFR for the whole population was 11±10% before and 5±7% after donation (p<0.001 before vs. after). As shown in Figure 1, before donation, reserve capacity was similar for the different BMI classes and the tertiles of age. respectively. After donation, however, reserve capacity was progressively lower with increasing BMI and increasing age (all ANOVA p≤0.01 respectively, see Figure 1). In obese donors, the response of GFR to dopamine did not reach statistical significance anymore, so post-donation reserve was no longer demonstrable (one-sample t-test p>0.10). This was not the case for donors in the highest tertile of age. When analyzed as a continuous variable, before donation, renal responses were not related to age or BMI. After donation, again, older age (r=-0.28, p<0.001) and higher BMI (r=-0.26, p<0.001) were negatively associated with the response of GFR to dopamine.

Combined effect of BMI and age on post-donation renal reserve

Older age and higher BMI are usually associated, so it is relevant to investigate both their independent and their combined effects. In our population, age positively correlated to BMI ($r=0.19$, $p=0.01$). When partial univariate correlation analyses were applied to correct for either BMI or age, the negative association remained intact between reserve capacity on the one hand and BMI or age on the other hand ($p=0.001$ and $p=0.008$, respectively). On multivariate analysis, both age ($p=0.001$) and BMI ($p=0.003$) were independent negative predictors of the GFR response to dopamine. The predictive power of this model was limited however, with R^2 of 0.13.

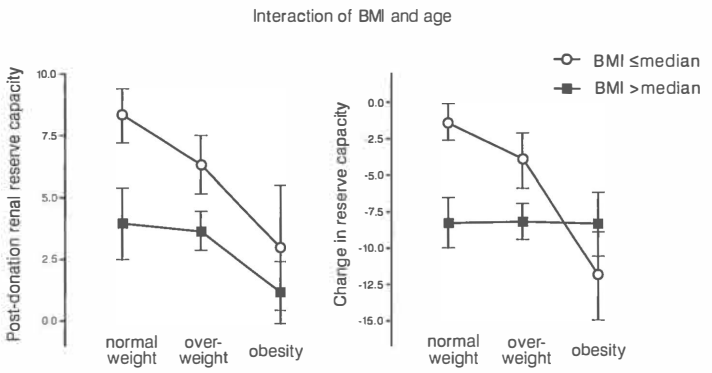
To illustrate the potential combined effects of age and BMI on reserve capacity, we plotted post-donation reserve capacity for four groups created by dividing first across median age (49 years) and second across median BMI of both groups obtained (24.2 kg/m² for younger donors and 25.8 kg/m² for older donors) as shown in Figure 2. Post-donation reserve capacity was lowest in donors who were both older and overweight. There was a statistically significant difference between donors with BMI below or above the median in the younger age group ($p=0.04$). In the older age group, however, there was no difference in RC between donors with or without overweight ($p=0.65$).

To quantify the combined effects of BMI and age on renal reserve capacity, BMI*AGE was analyzed as interaction term. On multivariate regression analysis, there was a statistically significant contribution for BMI and age as independent predictors for post-donation renal reserve, with a borderline significance for the interaction term BMI*AGE (see Table 2 for model). General linear modeling showed a significant interaction between BMI and age ($R^2=0.17$, $p<0.001$), with BMI in classes and age in tertiles.

Table 2 Multivariate analysis on BMI, age and their interaction predicting renal reserve capacity after living kidney donation

	Standardized ß	Significance
Body mass index	-0.93	0.026
Donor age	-1.15	0.032
Interaction BMI*age	1.28	0.083
	R^2 0.14; $p<0.0001$	

Figure 3 Interaction between age and BMI in influencing functional reserve of GFR and the donation-induced decrease in reserve capacity



The donation-induced decrease in reserve capacity is plotted for age below or above the median and different classes of BMI. Younger donors (age below median of 49 years) with normal weight (BMI below 25) had a statistical significant smaller decrease in reserve capacity compared to older donors with normal weight (p=0.005; post-hoc analysis). However, when overweight (BMI 25-30) or obesity (BMI≥30) was present, there was no longer a difference between younger or older donors. Furthermore, for younger donors, loss of renal reserve was profound when obesity was present (p=0.023 obese vs. normal weight donors with age below the median; post-hoc analysis). For older donors, body mass index did not influence the degree of loss of renal reserve.

Figure 3A shows the effect of overweight or obesity on renal reserve capacity by age group (cut-off at median age, ANOVA p=0.002). There was a statistically significant difference in RC between younger and older donors with normal weight (post-hoc p=0.005). However, when overweight or obesity was present, there was no longer a difference between younger and older donors (p=0.116 and p=0.594, respectively).

Determinants of the post-donation decrease in reserve capacity

On univariate analysis, both BMI (r=-0.22, p=0.003) and age (r=-0.20, p=0.006) were negatively correlated to the change in renal reserve capacity. Univariately, the interaction term BMI*AGE correlated to the decrease in RC (r=0.26, p=0.001). Multivariate regression analysis showed both factors to be independent determinants of the decrease in reserve capacity. On general linear modeling -entering BMI in classes and age in tertiles- the interaction term was a significant independent variable

in predicting post-donation renal reserve capacity (R2=0.14), with a p-value of 0.002. This is visualized in Figure 3B, which shows in a simplified model that BMI has considerable impact on the decline in reserve capacity in younger, but not older, donors.

Discussion

This study, the largest so far on renal reserve capacity before and after living kidney donation, confirms our hypothesis that the decrease in renal reserve after kidney donation is higher in older and overweight donors. Higher age and BMI were independently associated with a lower reserve capacity, whereas this was not the case in the same subjects prior to donation.

Renal reserve capacity after kidney donation has been studied in several prior, smaller studies (12-14,16,17). All studies document presence of reserve capacity after donation. Comparable to our results, renal reserve capacity tested with dopamine was found to be almost halved in kidney donors (12,13,16). This has been interpreted as a reflection of compensatory hyperperfusion and hyperfiltration of the remaining kidney. In our study, renal reserve after donation was reduced more in donors with advanced age and higher BMI. Moreover, we found post-donation reserve capacity of GFR to be completely annihilated in obese donors. So these factors, that were already documented to be associated with post-donation renal function impairment (10,18), are also associated with a marked reduction in renal hemodynamic reserve capacity, which may be due to a state of vasodilation as part of the compensatory response after unilateral nephrectomy. Long term renal monitoring would be important to investigate whether this response pattern after donor nephrectomy is associated with an increased risk for renal function loss.

Prior studies have reported a decrease in reserve capacity in older subjects, albeit not invariably so (4,8,9). In our large population, we did not detect an effect of age on reserve capacity prior to kidney donation. This may be due to the fact that kidney donors represent an above-average healthy subset of the population, in whom GFR was also relatively well-preserved, albeit lower than in younger subjects. Remarkably, donor nephrectomy elicited an age-related effect on renal reserve capacity. Effects of age on renal reserve have been attributed to impaired vasodilator response due to

arteriosclerosis in the kidney's interlobular and arcuate arteries (6). Apparently, in our older subjects, the condition of the renal vasculature allowed for an appropriate response do dopamine before donation. After donation, due to compensatory vasodilation elicited by the nephrectomy, further vasodilation capacity was limited, possibly explaining the underlying effect of age on renal reserve.

As to the effect of BMI, one prior study documented a reduced reserve capacity in obese hypertensives compared to lean hypertensives (7). Our study is the first to document an adverse effect of BMI on reserve capacity in normotensive subjects. Again, this effect was not present before donation, but was elicited by donor nephrectomy.

Previously, we found both higher BMI and age to be risk factors for renal function impairment, defined as a GFR below 60 mL/min/1.73 m^2 (or CDK stage III) (10). Now, we report on both factors to be associated with reduced post-donation renal reserve capacity. Impact of loss of renal reserve on long-term renal function in living kidney donors is currently unknown, but analyses are ongoing. Since higher BMI has in particular been associated with higher risk for renal damage after nephrectomy (18), our findings of a reduced post-donation renal reserve in kidney donors with higher BMI may be of clinical relevance. Finally, we observed that presence of overweight had more impact on loss of reserve capacity in younger donors. Younger donors with overweight or obesity displayed a loss of renal reserve that was similar to the loss of reserve of older donors which was irrespective of BMI. Moreover, in obese donors, the capacity to increase GFR to low-dose dopamine was annihilated after donation. Our current study design, with only a brief duration of follow-up after donation, does not allow to substantiate the clinical significance of this finding. Theoretically, absence of reserve capacity might be an unfavorable prognostic sign, indicating glomerular hyperfiltration, which could be harmful in the long run. Long-term follow-up studies are needed to document a possible effect of post-donation loss of reserve capacity in predicting long-term renal prognosis. In this respect, it is relevant to note that weight loss has been shown to correct obesity induced hyperfiltration (19), so a potentially favorable intervention is available.

We emphasize the need for donor follow-up especially when obesity is involved in younger donors, since these donors are potentially exposed to an increased renal risk

for a long period of time. Though a potential benefit from weight loss, low protein diet and/or ACE inhibition remains to be investigated, weight loss should be stimulated in donors with excess body weight.

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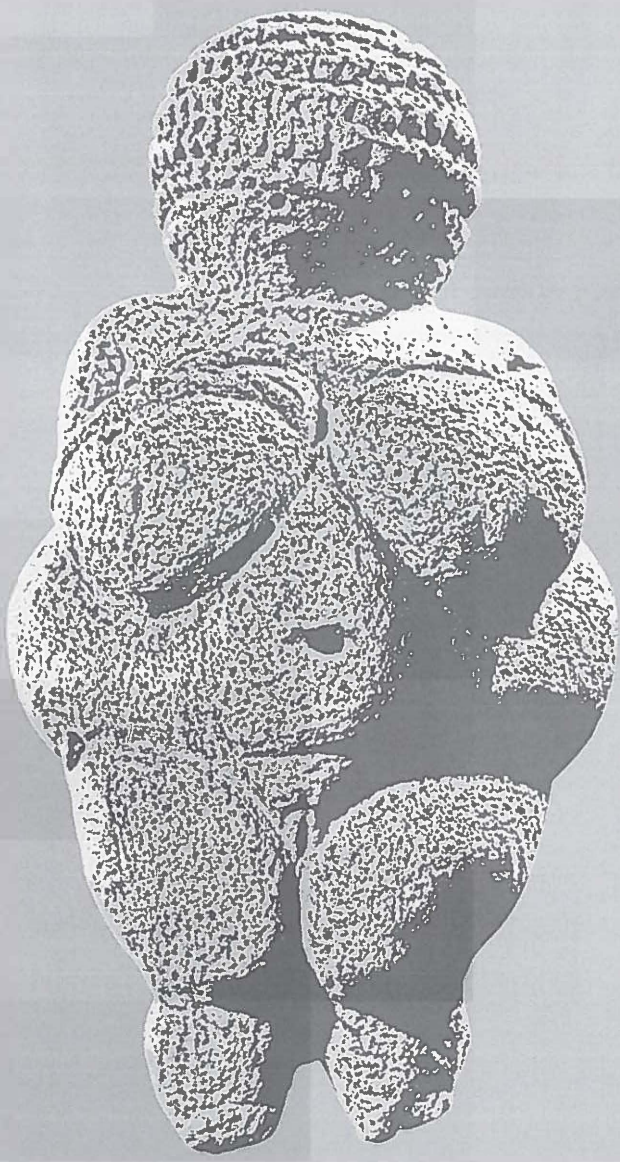

General discussion and summary

Chapter 6

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Modified from: Obesity and renal hemodynamics. Contrib Nephrol. 2006;151:184-202

Introduction

The studies described in this thesis were motivated by the increasing recognition that obesity is a risk factor for renal damage in native kidney disease (1-3) and in renal transplant recipients (4-9). Several factors that are usually associated with obesity, such as hypertension, insulin resistance and diabetes, are likely to be involved in the increased renal risk in obesity. However, also in the absence of these factors, obesity is associated with an unfavourable renal hemodynamic profile that may play a role in the susceptibility and progression of chronic renal damage. More specifically therefore, this thesis focuses on the renal hemodynamic profile in overweight and obesity in man, and its possible impact on renal risk.

As discussed in **Chapter 1** the prevalence of overweight and obesity has dramatically increased in the last two decades. Obesity seems to become the major health problem of the 21st century as it is associated with increased morbidity and mortality, mainly due to an elevated cardiovascular risk, with insulin resistance and diabetes, dyslipidemia and hypertension as most important risk factors. However, obesity is also a risk factor for renal damage - in native kidney disease (1-3), in renal transplants (4-9) and after uninephrectomy (10). Considering the pandemic of obesity and overweight, therefore, weight excess may turn out to become the main risk factor for renal damage in the decades to come.

In this final chapter the studies described in this thesis will be put into the wider perspective of the currently available data on the impact of obesity and overweight on renal hemodynamics, with the main emphasis on human data. We will discuss its possible underlying mechanisms and the implications for long-term renal risk. Finally, we discuss interventions that have potential to limit the renal risks of obesity.

Measurement of renal hemodynamics

Measurement of renal hemodynamics by clearance techniques

Current evidence on the role of renal hemodynamics as a factor in progressive renal function loss has mainly been derived from rat studies, where micropuncture allows direct assessment of glomerular flow and pressure. In remnant kidney models it has convincingly been shown that changes in renal hemodynamics leading to glomerular

hypertension are important pathogenetic factors in progressive renal damage (11-15). In animal models of obesity it has been shown that alterations in the glomerular microcirculation resemble those after renal ablation, with glomerular hypertension and hyperfiltration at the single nephron level (16;17), as will be discussed in more detail in the next paragraph.

In humans on the other hand glomerular flow and filtration pressure cannot directly be measured. Current knowledge on renal hemodynamics in man is therefore derived from indirect assessment of renal hemodynamics by clearance techniques. Accurate assessment of glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) can be obtained by measuring the renal clearance of specific markers, such as ^{125}I-iothalamate, ^{99m}Tc-diethylenethiaminepenta-acetic acid, ^{51}Cr- ethylenediaminetetra-acetic acid, or inulin for GFR, and ^{131}I-hippurate or para-amino-hippuric acid for ERPF, respectively. When GFR and ERPF are measured simultaneously, filtration fraction (FF) can be calculated as the ratio from GFR and ERPF. FF can be a helpful parameter to interpret changes in GFR in terms of the underlying hemodynamic changes. When a rise in GFR is primarily related to hyperperfusion, it will be associated with a proportional rise in ERPF and thus unaltered FF. When a rise in GFR is primarily due to a change in filtration pressure, this will be apparent as a rise in FF, as ERPF will be elevated less than GFR. A rise in filtration pressure is assumed to be unfavourable in terms of long term renal risk, as longstanding glomerular hypertension was proven to be involved in progressive renal damage in numerous animal studies. These data are supported by indirect evidence in human studies as well, demonstrating the prognostic impact of changes in FF during therapy for long term renal outcome (18;19). For these reasons, FF is considered a surrogate parameter for glomerular hypertension in man.
It should be mentioned, however, that GFR measurements in man can be misleading in the assessment of glomerular hyperfiltration, as clearance measurements reflect the total filtration rate of all nephrons together, so a GFR within the normal range may reflect a normal pressure/GFR in a normal nephron number, but also an elevated pressure/GFR in a decreased number of nephrons without a possibility to distinguish between these conditions. Only if GFR is elevated, one can be sure that single nephron GFR is elevated as well.

Estimation of renal function by using creatinine-based equations

Measurement of GFR by specific tracers is expensive and time consuming. Therefore,

for clinical and epidemiological purposes GFR is usually estimated from serum creatinine by renal function equations that include antropometric indices such as age, weight and gender to account for between-individual differences in muscle mass and the consequent differences in creatinine generation. Many equations are available, mostly empirically developed in populations with native kidney disease (20-37). However, these equations are subject to bias that can substantially confound evaluation of the association between obesity and renal function, as in obesity a higher body weight is usually associated with a higher fat mass, but not a higher muscle mass, whereas the weight-factor in the equation is assumed to reflect muscle mass. In **Chapter 2** we evaluated this bias in transplant recipients, showing that, at higher BMI, the MDRD equation progressively underestimated, and the Cockcroft-Gault equation progressively overestimated GFR. Presence of BMI-dependent bias is in line with data in native kidney disease. In a relatively small population, the Cockcroft-Gault equation underestimated GFR at low BMI, and overestimated GFR at high BMI, whereas for the MDRD equation the BMI-dependent bias was of borderline significance, and the recently developed equation by Rule showed progressive overestimation of GFR at high BMI (34). Thus, bias in the equations by Cockcroft-Gault and Rule can erroneously suggest presence of hyperfiltration at high BMI (38)! These shortcomings hamper the interpretation of epidemiological analyses of the association between obesity and renal function. Currently, the MDRD equation has become the standard for estimation of GFR, as its overall predictive performance in different populations is better than for other equations, but it is recognized that better equations are warranted.

Another issue relevant to renal function estimates in obesity is the normalization of data to body surface area (BSA). This applies to renal function equations as well as accurate renal function measurements. Renal function indices are usually expressed per 1.73m² BSA, as standard reference body size. However, excess weight does not only lead to a rise in BMI, but also to a rise in BSA. Thus, when an individual gains weight, BSA-normalized kidney function would "decrease", in the absence of a true change in renal function. Likewise, BSA-normalization may confound comparisons between obese subjects and non-obese control populations, as illustrated by Schmieder et al who found a lower BSA-corrected ERPF in obese subjects compared to lean subjects (39), whereas height-corrected and uncorrected ERPF were not different. Similar findings, also for GFR, were shown by Anastasio et al (40). For these reasons it has been proposed that normalization for height would be more appropriate, albeit no consensus

Table Human studies on overweight and obesity and renal hemodynamics

Ref.	N	Population	BMI	GFR	ERPF	Normalization for	Renal hemodynamics in obese subjects vs non-obese controls
(105)	42	HT	31	-	hippurate	height	↑ RBF in normotensive and hypertensive obese
(41)	60	HC/HT Obese, non-obese	32	Tc-DTPA	hippurate	height	↑ GFR and ↑ ERPF in obesity, ↑ FF in HT obese only
(46)	64	HC/HT	34	Tc-DTPA	hippurate	-	ERPF↓ and ↑ FF in centrally obese HT
(48)	45	Healthy moderately obese	29	-	xenon	kidney volume	↑ RBF in obese, on low sodium diet only
(40)	20	Severely overweight, normotensive	47	inulin	hippurate	BSA	No differences
(2)	12	Severely obese with IR	44	inulin	hippurate	-	↑ GFR; ↑ ERPF; ↑ FF
(45)	8	Severe obesity/IR, Weight reduction	48	inulin	hippurate	-	↑ GFR; ↑ RPF; ↑ FF correction by weight loss
(106)	102	Healthy	24	iothalamate	hippurate	BSA and height	↑ FF with higher BMI

N number of overweight/obese patients
HC healthy controls
HT hypertensive subjects
IR insulin resistance
BMI body mass index
GFR glomerular filtration rate
ERPF effective renal plasma flow
RBF renal blood flow
BSA body surface area

exists as yet (41). For analysis of the studies described here we used uncorrected values of GFR and ERPF, as well as values corrected for height. At any rate, filtration fraction (FF), the ratio of GFR and (E)RPF, is not affected by the adopted method of normalization, and can be interpreted to reflect true differences between obese and non-obese subjects.

Impact of obesity on renal hemodynamics

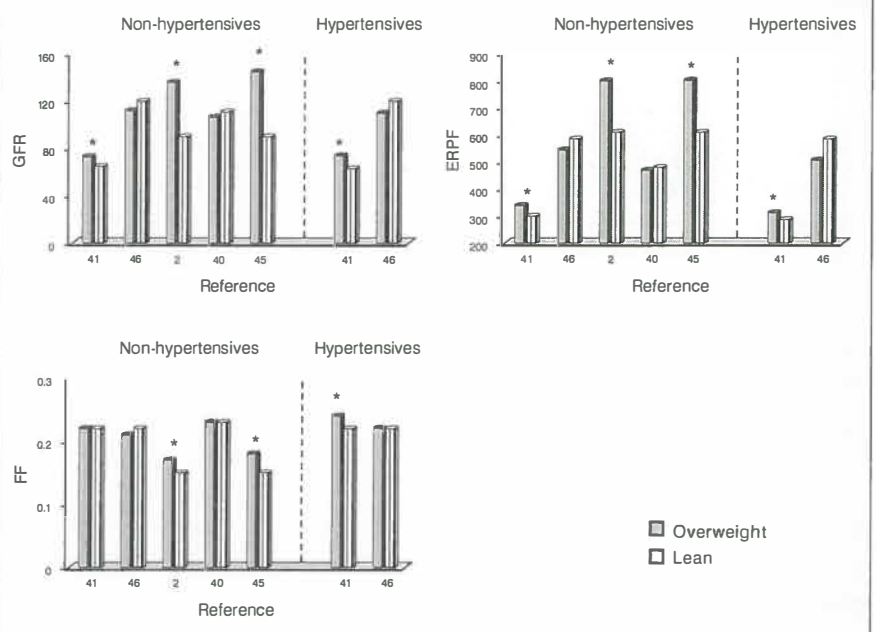
Several experimental studies addressed the impact of obesity on renal hemodynamics. Multiple studies were done in obese Zucker rats, a genetic model of obesity associated with slowly progressive renal damage, proteinuria and focal glomerulosclerosis.

Micropuncture studies (16;17;42;43) revealed an elevated GFR, which was attributable to an increased single nephron plasma flow rate as well as glomerular transcapillary hydraulic pressure. The elevated GFR, however, was not a prerequisite for the development of structural damage in this model (42;43). Also, in diet-induced animal models of obesity, an elevated GFR is usually documented (44).

Human studies on the impact of obesity and overweight on renal hemodynamics, including our own analysis from **Chapter 3** in healthy subjects, are summarized in the Table. To avoid the BMI-dependent bias inherent to renal function equations, only studies using accurate clearance methods are included here. It shows that an elevated GFR was found in most, but not all studies. Frequently, but not always, this was accompanied by an elevated ERPF and/or an elevated FF. From measuring dextran sieving curves, and entering these data in a theoretical model on the determinants of filtration, Chagnac et al could attribute the elevated GFR in severe obesity to an increase in transcapillary hydraulic pressure, ΔP (2). A more recent study of this group is of special interest as well, as it provides renal hemodynamic data before and after weight loss by bariatric surgery (45). A massive weight loss of 48 kg in nine morbidly obese, non-diabetic subjects over a period of 12-17 months, with a decrease in mean BMI from 48 to 32 kg/m², resulted in a decrease in GFR of 145±14 to 110±7 ml/min (versus 92±4 ml/min in controls), with corresponding decreases in RPF, FF, albuminuria, and blood pressure, along with improvement in insulin resistance.

For the five studies that analyzed both GFR and renal perfusion (41;46;2;40;45) in obese subjects and controls an overview of the mean values for GFR, ERPF and FF is given in Figure 1, ranked by BMI (from left to right). For the two studies that provide data for hypertensives separately (41;46) data are given by a break-up by presence or absence of hypertension. The overview shows that in the studies reporting a difference between obese and non-obese subjects, the difference is usually in the same direction, namely hyperfiltration (elevated GFR), hyperperfusion (elevated ERPF) or elevated glomerular pressure (FF). In two of the studies an effect of obesity was present only under specific conditions. In the study by Ribstein et al obesity was associated with altered renal hemodynamics in hypertensive, but not in normotensive subjects (41), and in the study by Scaglione FF was elevated (and renal plasma flow reduced) in hypertensives with central obesity (presumably reflecting insulin resistance) only, but not in normotensive subjects with central or peripheral obesity, or in hypertensives with

Figure 1

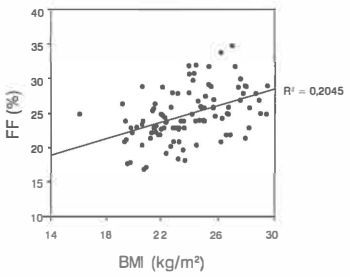


Five studies (41;46;2;40;45) showing the impact of overweight and obesity on glomerular filtration rate (GFR), effective renal plasma flow (ERPF) and filtration fraction (FF) respectively. Bars left of dashed line show non-hypertensive subjects, bars right of dashed line show the hypertensive subpopulation of study 1 and 2.

6

peripheral obesity (46). These data illustrate the relevance of the interaction between obesity/overweight and its frequent co-morbid conditions such as hypertension and insulin resistance for renal hemodynamics. The presence of hypertension may result in differences in ERPF in particular as in established hypertension usually a decreased ERPF is found, with a preserved GFR, and consequently and elevated FF (47). Thus, as to FF the effects of hypertension and obesity are in the same direction, but as to ERPF their effects are opposite. Moreover, sodium intake may be relevant as well; Porter et al found an elevated renal plasma flow in moderately obese, healthy hypertensives as compared to normotensive controls during a severe dietary sodium restriction, but not during a liberal sodium diet (48). The mechanism underlying this effect of sodium status has not been established.

Figure 2



Scatterplot showing the univariate correlation between body mass index (BMI) and filtration fraction (FF) in healthy subjects. Adapted from Bosma et al (106).

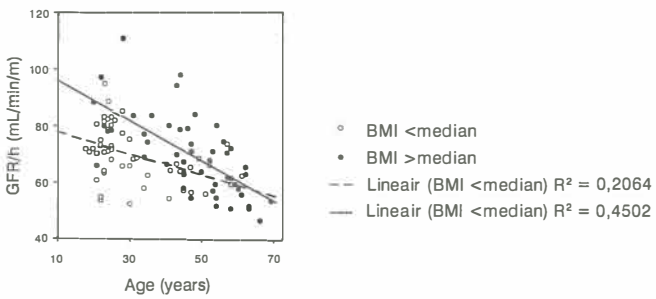
Overweight and obesity can modulate renal hemodynamics also in the absence of co-morbid conditions, as apparent from the other studies in Figure 1. Our own data (**Chapter 3**) provides strong evidence for an independent role of weight excess. We found a relationship between a higher BMI and a higher FF in a population of normal subjects, well-documented to be healthy and with a BMI not exceeding 30 kg/m² (Figure 2). This demonstrates, first, that excess weight is associated with altered renal hemodynamics even in the absence of overt obesity without an apparent lower threshold, and second, that the impact of weight excess on glomerular hemodynamics does not depend on presence of co-morbid conditions. Nevertheless, as apparent from the above studies, when hypertension and/or insulin resistance are concomitantly present, their renal manifestations may interact with those of the excess weight, and thus account for some of the discrepancies between studies.

It should be noted that many other factors can modulate the effects of overweight and obesity on renal hemodynamics as well. These include age (49), sodium intake, drug use, and possibly also the severity of obesity, although the overview in Figure 1 does not support the latter. The respective effects of age and BMI on GFR are illustrated in Figure 3, showing cross-sectional data in healthy subjects. BMI-associated hyperfiltration was only present in young adults but in older subjects GFR was similar for those with a BMI above or below the median. This suggests a steeper age-related decline in

subjects with higher BMI, but also that BMI-associated hyperfiltration in young adults is relatively innocent in terms of renal risk at an older age. However, these are cross-sectional data, in selected healthy subjects with a BMI not exceeding 30 kg/m². A proper interpretation in terms of presence of absence of long-term renal risk induced by hyperfiltration would therefore require longitudinal data, also in subjects with the usual co-morbid conditions.

It should be noted moreover, that the renal hemodynamic status in adults and older subjects also depends to a considerable extent on their prior medical history as regards longstanding hypertension and cardiovascular disease and the resulting presence of subtle renal end organ damage (49;50). Obviously, this is all the more true for population with an underlying primary renal condition. Whether BMI modulates renal hemodynamics in patients with a primary renal disorder would be of great interest, but has not been investigated so far. For renal transplant recipients we investigated the impact of obesity on renal hemodynamics as described in **Chapter 4**. It is well-recognized that a higher BMI of the recipient is associated with renal risk after renal transplantation (4-9). Whether this increased renal risk is due to altered renal hemodynamics, i.e. a hyperfiltration pattern in the transplanted kidney, was so far

Figure 3



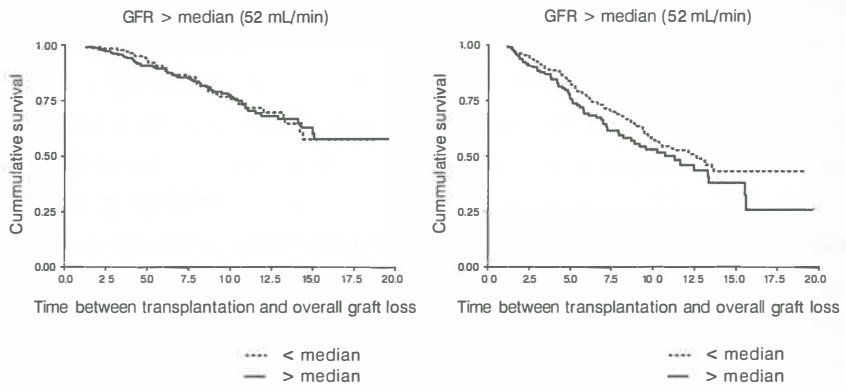
Scatterplot showing the association between age and GFR in a healthy study population with a break-up by median BMI (median 23.9 kg/m²), showing a more steep decline with age in subjects with higher BMI, mainly due to a higher GFR at younger age. Note that GFR is presented in mL/min per meter of height. Adapted from Bosma et al (106).

unknown. It was not known whether BMI is relevant to renal hemodynamics in renal transplants in the first place. It should be emphasized that extrapolation of data from native kidneys to transplanted kidneys would not be justified, as in the renal transplant many other factors are present that could affect renal hemodynamics and thus overrule an effect of BMI, if any. These include use of calcineurin inhibitors, the single kidney state and presence of intrinsic renal damage. Of note, as opposed to native kidneys, the transplanted kidney is denervated. Furthermore, the transplanted kidney provides an interesting model system, as the genetic backgrounds of the kidney and the recipient are different. Thus, for various reasons it would be relevant to establish whether a higher recipient BMI is associated with a specific hemodynamic profile in the transplanted kidney. Moreover, it would be interesting to know whether the association between higher BMI and worse renal outcome can be attributed to altered renal hemodynamics. These questions were addressed in **Chapter 4**, in which we describe a cross-sectional association between BMI and renal hemodynamics in a large population of renal transplant recipients, with evaluation at 1 and 5 years after transplantation respectively. In line with the data in the healthy subjects described in **Chapter 3**, we showed an impact of BMI on GFR and FF in the transplant population as well, with a higher GFR and FF at one year after transplantation in recipients with a higher BMI. The impact of BMI on renal hemodynamics was not explained by the presence of overt diabetes mellitus. Survival analysis revealed that a lower GFR and a higher FF were independent determinants of overall graft loss and graft loss by patient mortality. Lower GFR and higher BMI were determinants of death-censored graft loss, with a contribution of a higher FF as well. To our knowledge, this is the first study demonstrating the predictive effect of a higher FF for a worse long term renal outcome in man. So far, in human the evidence for an independent pathogenetic role of renal hemodynamics was of an indirect nature (18;19). As shown in Figure 4 for a given (low) GFR, in subjects with a higher FF long term outcome is worse than in subjects with a low FF, i.e. subjects in whom filtration rate is obtained at a lower filtration pressure. It would be highly interesting to have similar data for native kidney disease, but so far, such data are not available.

Measurement of renal reserve capacity

As noted above, for the purpose of detecting hyperfiltration the interpretation of whole kidney clearance measurements can be cumbersome and hyperfiltration at the single nephron level cannot be excluded if GFR is normal or decreased. Therefore, additional

Figure 4



Overall graft loss in 838 renal transplant recipients (mean age 45±13 years, 58% male, mean BMI 26±4), stratified for GFR (higher and lower than median, respectively). All recipients were transplanted between 1984 and 2002 with a mean overall graft survival of 8.2±4 years. Data are shown by median of FF. Data adapted from Bosma et al (107).

strategies have been developed to address the issue of hyperfiltration. These strategies start from the assumption that a decrease in filtration reserve is a sign of hyperfiltration. The normal kidney has a considerable filtration reserve, as for instance apparent from the immediate rise in GFR and ERPF in the remaining kidney after donation, from the considerable rise in GFR and ERPF in pregnancy, and from the responses to several renal vasodilators. Several protocols have been developed to assess the reserve of filtration and perfusion, respectively, from the renal responses to specific renal vasodilators, alone or in combination (51-53). In our centre, the renal responses to dopamine, amino acids and their combination has been routinely in use for a long time for this purpose. Dopamine elicits preferential efferent vasodilation (resulting in a rise in ERPF that exceeds the rise in GFR), whereas amino-acids give predominantly afferent vasodilation, resulting in a prominent rise in GFR, with a less prominent or unchanged ERPF. The combination of the two gives both afferent and efferent vasodilation and marked increases in GFR and ERPF that exceed those with the two separate compounds. Renal reserve filtration capacity may be relevant for maintenance of renal function after loss of functional renal mass by disease, or after kidney donation. In this concept, loss of nephrons, by for instance kidney donation, or by the aging process,

would be associated with reduction of renal reserve capacity by using the available reserve for maintenance of renal function. Moreover, hyperfiltration could be hypothesized to be unmasked by a loss of reserve capacity, and accordingly absence or decrease of filtration reserve could be a marker of sustained single nephron hyperfiltration that may have maladaptive consequences by damaging remnant glomeruli. To see whether the renal hemodynamic pattern associated with weight excess might reflect hyperfiltration, we investigated the association between BMI, renal hemodynamics and renal reserve capacity, as discussed in **Chapter 5**. We tested whether a higher BMI would be associated with a decrease in renal reserve capacity, before and after donation, also addressing other factors that may affect renal reserve capacity, such as older age and loss of nephrons by uninephrectomy. To this purpose we measured renal hemodynamics and renal reserve capacity before and after kidney donation, with analysis for determinants of reserve capacity and showed that, after donation, a higher BMI was associated with a renal hyperfiltration profile. Higher BMI was not associated with a decrease in renal reserve capacity before donation. Thus apparently, kidney donation unmasks hyperfiltration in subjects with higher BMI. We furthermore found that older age, as another possible factor that might decrease reserve capacity, was a predictor for predonation FF, however not for FF after donation.

Mechanisms underlying the obesity-related changes in renal hemodynamics

Together, the above data suggest that obesity and overweight are associated with an altered afferent-efferent glomerular vasomotor balance. A decreased afferent arteriolar tone is present, that allows a larger transmission of the systemic arterial pressure to the glomerular capillary bed (54) and an increase in filtration as well as perfusion. When combined with a relative increase of efferent arteriolar tone the rise in filtration is more prominent than the rise in perfusion, as apparent from an elevated filtration fraction. The elevated glomerular transcapillary hydraulic pressure as calculated by Chagnac et al (2) is in line with this assumption. Extracellular volume expansion, due to the obesity-associated increase in sodium reabsorption, can also be expected to contribute to renal hyperperfusion and hyperfiltration. Furthermore, glomerulomegaly, as documented in obesity-related focal glomerulosclerosis (55), should be considered as a possible factor involved in the hyperfiltration and hyperperfusion of obesity. However, data on glomerular morphology are available only from subjects in whom proteinuria and renal function impairment warrant a renal biopsy, and no data are available to substantiate this assumption for subjects with less severe renal involvement.

Insulin resistance

Excess weight gain, especially when associated with visceral obesity, leads to glucose intolerance, insulin resistance and a compensatory hyperinsulinemia (56), which has been associated with sodium retention as well as increased glomerular filtration rate (2;57). Dengel et al demonstrated a close correlation between insulin resistance and renal hemodynamics in obese, mildy hypertensive, older subjects (58), in whom a lower glucose disposal rate during hyperinsulinemic euglycemic clamping correlated with a higher GFR and FF. This association was blunted by a high sodium diet, i.e. a condition of suppression of the renin-angiotensin system. The mechanism underlying the link between insulin resistance and renal hemodynamic alterations in obesity has not been elucidated yet. Hyperinsulinemia has been suggested to be involved by its stimulating effects on sympathetic nervous system activity and vasoconstrictor effects (59-62). However, experimental hyperinsulinemia does not lead to elevated FF, neither in acute nor in chronic experiments (57;63;64). Whereas the effects of exogenous insulin in an experimental set-up may not be completely similar to those of endogenous hyperinsulinemia, this renders a direct effect of high insulin levels less likely, and indirect effects, by associated factors, are presumably involved. Indirect evidence from epidemiological data suggests that the effects of insulin resistance, as estimated from presence of a central fat distribution, can dissociate from those of overweight. In the general population-based PREVEND cohort, obesity was associated with hyperfiltration, whereas a central fat distribution was associated with a greater risk for mild renal function impairment not only in obese, but also in lean subjects (65). Thus, the renal risks of obesity may be related more closely to the concomitant presence of insulin resistance rather than with the obesity as such.

Renin-angiotensin system

Several lines of evidence suggest the renin-angiotensin system (RAS) to be involved in the renal hemodynamic changes in obesity. First, circulating components of the RAS are elevated in obesity in experimental animals (66) as well as human. In this respect, activation of the RAS in adipose tissue has been proposed to provide a link between obesity and hypertension (67) by production of angiotensinogen – the substrate for renin - by adipose tissue (68). The resulting generation of the effector hormone angiotensin II can elicit hypertension by its vasoconstrictor effects on the peripheral vascular bed and by promoting tubular sodium reabsorption. Moreover, in the kidney it will elicit efferent vasoconstriction, as manifest from a rise in filtration fraction. Several

studies reported correlations between plasma angiotensinogen concentrations, blood pressure and BMI (69-71). Moreover, (72) an effective weight loss program reduced circulating angiotensinogen, plasma renin activity, aldosterone and ACE activity, as well as adipose tissue expression of angiotensinogen. In humans, Scaglione et al (46) found significantly higher plasma renin levels in centrally obese normotensive subjects compared to peripheral obese and lean subjects. Ruano et al (73) retrospectively studied 100 morbidly obese patients, split up for central and peripheral obesity. In the centrally obese patients they found higher levels of plasma renin activity, aldosterone and ACE with sodium retention, potassium loss and high insulin levels. After gastric bypass these abnormal hormone levels tended to normalize. Hopkins et al showed a blunted renal vascular response to angiotensin II infusion in subjects with higher BMI, suggesting increased intrarenal RAS activity as well (74). In line with this, a study in mice showed that obesity was associated with a tissue-specific increase in ACE activity in the kidney (75), but otherwise data on the intrarenal RAS are scarce.

The renal impact of increased activity of the RAS can also be inferred from the renal hemodynamic response to RAS-blockade. The renal vasodilator responses to RAS blockade were shown to be directly proportional to BMI in two studies. In 100 healthy, normotensive, predominantly overweight and obese subjects (76) a highly significant relationship was found between the age- and plasma renin activity-adjusted BMI and the renal plasma flow response to captopril, supporting the assumption that a BMI-associated higher intrarenal RAS activity is involved in renal vascular tone in overweight and obesity. A similar relationship was found by Price (77) in 12 type II diabetic patients with a wide range of BMI, in whom the rise in RPF elicited by angiotensin-receptor blocker irbesartan was directly proportional to BMI, with BMI accounting for 50% of the variation in the renal hemodynamic response. These BMI-dependent renal effects of RAS-blockade also suggest that RAS-blockade may be a suitable tool to reduce the renal risks of obesity - assuming that the renal hemodynamic profile reflects a long-term risk.

In accord with this assumption, RAS-blockade was shown to reduce proteinuria in obese proteinuric patients. Interestingly, in a small study weight loss was as effective as RAS-blockade in reducing proteinuria (78). Whether the antiproteinuric effect of weight loss relates to renal hemodynamic changes has not been established, but theoretically, the reduction in GFR and FF that would be anticipated to occur with weight loss can be expected to lead to reduction of proteinuria.

Interaction between renal sodium handling and renal hemodynamics in obesity

Altered tubular sodium handling can affect renal hemodynamics by the tubuloglomerular feedback (TGF) mechanism. TGF regulates glomerular hemodynamics by modifying afferent arteriolar tone in response to changes in NaCl delivery to the macula densa. A lower distal NaCl supply elicits a decrease in afferent tone, thus eliciting a rise in glomerular filtration pressure and filtration rate. The ensuing rise in filtered load then restores NaCl supply to the macula densa towards its original level (79). Obesity is well-established to be associated with increased sodium reabsorption (80-82), presumably at the level of Henle's loop. Increased TGF activity can thus contribute to the afferent vasodilation observed in obesity.

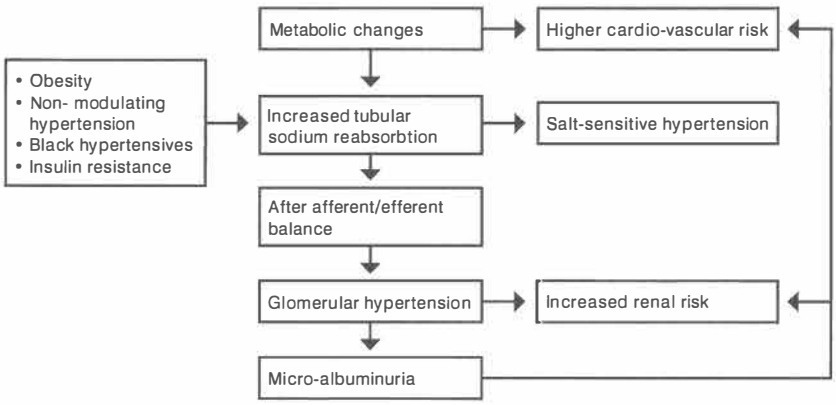
The increase in FF might well be involved in this increased sodium reabsorption, as this alters the Starling forces in the peritubular capillaries towards increased sodium reabsorption. Recent data, published in abstract form (83) support that the elevated FF in obesity is involved in the impaired capacity to excrete excess sodium.

Interestingly, the impaired sodium excretion in obesity is also related to an impaired pressure natriuresis response, in particular in central obesity (76;84;85), and has been attributed to increased activity of the RAS, of the sympathetic nervous system (76;86-88), hyperinsulinemia (89), as well as to compression of the kidneys by excess retroperitoneal adipose tissue (90) – and results, with elevated FF, in a vicious circle. The impaired sodium excretion of obesity can be considered to act as a two-edged sword. First, it contributes to volume expansion and obesity hypertension. The latter is well established to be sensitive to sodium intake, and interestingly, the sodium-sensitivity of blood pressure is attenuated by weight-loss (88). Second, by its effect on afferent tone it impairs the glomerular protection against elevated systemic pressure. This provides a very plausible candidate mechanism for the renal susceptibility in obesity hypertension, although for obvious reasons no human data are available to support this assumption.

The combination of sodium-sensitive blood pressure and an unfavourable renal hemodynamic profile is not unique to obesity. It is also observed in sodium-sensitive black hypertensives (91), non-modulating hypertension, and sodium-sensitive hypertensives with an unfavourable cardiovascular risk profile and micro-albuminuria (92-95), conditions that appear to share an elevated cardiovascular risk as well, and that also display a considerable overlap (Figure 5). Of note, in these conditions the unfavorable

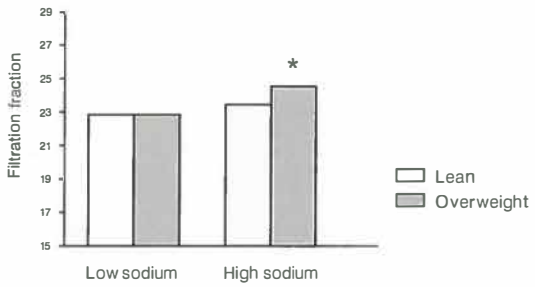
renal hemodynamic profile is elicited, or aggravated by high sodium intake (96). Recent data from our own group demonstrated that also in overweight, in otherwise healthy young subjects, high sodium intake (12 g/day) elicits a hyperfiltration pattern, with an elevated FF and GFR. In these subjects, remarkably, the overweight-associated hyperfiltration was abolished by a moderate (3 g/day) restriction of dietary sodium (Figure 6). So apparently, sodium and weight excess interact as regards renal risk profile, and a poor profile is found only when both are simultaneously present. The maladaptation to high sodium may be worthwhile to consider for its clinical implications. Whereas in obesity the main dietary measures should obviously be aimed at weight reduction, moderate dietary sodium restriction may be a useful adjunct to improve the obesity-associated renal risk profile, all the more so because hypertension in obesity is usually sodium sensitive. As the data by Porter (48;58) however suggest that the renal hemodynamic abnormalities of obesity can be unmasked, or promoted by a severe sodium restriction of around 1 g/day, the renal hemodynamic effects of dietary sodium restriction in obesity warrant further study.

Figure 5



Schedule depicting the alleged pathogenetic relationships between renal sodium handling, renal hemodynamics, sodium-sensitive hypertension, and cardiovascular and renal end-organ damage in obesity and other conditions.

Figure 6



Interaction between weight excess and sodium intake on renal hemodynamics. Filtration fraction (GFR/ERPF, expressed in %) in 95 healthy young men, measured during low (50 mmol Na^+/day) and high (200 mmol Na^+/day) with subjects as their own control, with a break-up by BMI. Lean: n=77, BMI<25 kg/m² (mean BMI 22.1±1.4); overweight: n=18, BMI<25 kg/m² (mean BMI 26.9±2.4). In lean subjects high sodium did not induce a rise in FF, but in overweight subjects high sodium induced a significant rise in FF ($p<0.05$). As a consequence, FF was significantly higher in the overweight subjects during high sodium only. Data adapted from Krikken et al (108).

Leptin and the sympathetic nervous system

Other mechanisms suggested to be involved in the renal effects of obesity are increased activity of the sympathetic nervous system, and elevated leptin levels. Increased activity of the sympathetic nervous system is well-documented in obesity (80;97;98), and studies in experimental animals have shown its involvement in the sodium-retention and hypertension of obesity (80). However, its role in the obesity-associated changes in renal hemodynamics is not well documented. Leptin, an adipocyte-derived hormone that is involved in the regulation of weight by effects on appetite and energy expenditure, leads to sympathicoactivation of the kidneys and adrenal glands, suggesting that the obesity-associated increase in sympathetic nerve activity could be due in part to these sympathetic effects of leptin (97;98). Human obesity is often associated with leptin resistance, providing sympathetic underactivity with subsequent positive energy balance and weight gain. However, leptin resistance does not lead to sympathetic underactivity in the kidneys, as shown by Rahmouni et al (99). They examined the role of leptin in hypertension associated with diet-induced obesity in mice and demonstrated a preservation of the renal sympathetic but also of arterial pressure response to leptin, which could be a candidate mechanism for the elevated

cardiovascular risk in obesity. The other way round leptin deficiency, as in the ob/ob mouse, leads to decreased arterial pressure, despite severe obesity (100). Whereas these results support a role for leptin in obesity hypertension, however, leptin does not seem to exert a clear cut effect on renal hemodynamics (11).

Implications of altered renal hemodynamics in obesity

As already noted above, the altered renal hemodynamics in obesity can be considered one of the factors underlying sodium retention and sodium-induced hypertension in obesity. Moreover, by analogy with diabetic hyperfiltration and with remnant kidney models in experimental animals (11-14;17), the renal hemodynamic profile with glomerular hyperfiltration and hypertension in obesity is assumed to be a pathogenetic factor in the susceptibility to progressive renal function loss by hypertensive glomerular capillary damage and the ensuing increased albumin leakage (2). In micropuncture studies in obese Zucker rats the elevated glomerular pressure precedes the development of focal sclerosis (17), but in other studies glomerular hyperfiltration was not a prerequisite for the development of structural renal damage (42;43), suggesting that renal hemodynamic changes are not a crucial pathogenetic factor in this model. Moreover, RAS blockade protects against focal sclerosis in this model without affecting renal hemodynamics (17), so the pathogenetic role of the renal hemodynamics in obesity-associated renal damage is not straightforward, and presumably involves interaction with other obesity-associated factors.

In human, in spite of the recognition of obesity as an increasingly important renal risk factor (101), until recently no longitudinal data were available to document a pathogenetic role of renal hemodynamics in the elevated renal risk of obesity. This was simply due to the paucity of populations with solid data on renal hemodynamics as well as long term follow-up. The data described in **Chapter 4**, in the transplant population, provide the first evidence that a renal hemodynamic profile with glomerular hyperfiltration, as apparent from a higher FF, is a determinant of graft loss, independent of hypertension, proteinuria and diabetes mellitus. These data still require confirmation in native kidneys. Nevertheless they strongly support the assumption that the obesity-associated renal hemodynamic profile increases the renal susceptibility to hypertensive damage, by combined effects of afferent vasodilation with impaired protection against elevated systemic arterial pressure, and an elevated efferent vascular tone that further increases glomerular pressure. Considering the usual co-existence of obesity and

hypertension this alleged mechanism warrants further exploration. It is supported by the association of obesity, glomerular hyperfiltration and albuminuria in many experimental and clinical studies (2;102). The potential of RAS-blockade to alleviate the renal hemodynamic consequences of obesity, along with a reduction in blood pressure, suggests that RAS-blockade may be a fruitful intervention to reduce the long term renal risks of obesity, an assumption that is supported by its beneficial effects on obesity-associated proteinuria (103). Intriguingly, a higher FF was also a determinant of patient mortality, again independent of glomerular filtration rates, proteinuria and blood pressure. The mechanism underlying this association could not be derived from the available data. It might well be that an elevated FF reflects mechanisms that can lead to cardiovascular mortality, such as increased neurohumoral activation, but further studies are definitely needed to unravel the possible pathogenetic mechanisms that link FF with mortality.

Conclusions and directions for the future

Obesity and overweight are associated with altered renal hemodynamics, usually characterized by elevated filtration that can also be associated with elevated perfusion, elevated filtration pressure, or both, and leading to sodium retention and sodium-induced hypertension in obesity. We found that this unfavourable renal hemodynamic profile is a predictor of graft loss in renal transplant recipients, supporting its pathogenetic impact. Taken together with analogous data in diabetes and other hyperfiltration conditions, these findings suggest that an obesity-associated renal hemodynamic profile contributes to the elevated renal risk in obesity, in interaction with other obesity-associated factors like hypertension and insulin-resistance. In short-term studies the renal hemodynamic alterations in obesity and the associated proteinuria were reversible by weight loss, sodium restriction, and by RAS-blockade, respectively. These interventions are therefore likely to have the potential to limit the renal risks of obesity, and deserve to be explored in long term intervention studies, as adjunct measures to weight reduction. The effects of novel weight loss regimens based on cannabinoid CB1 receptor antagonism (104) on renal hemodynamics and renal risk remain to be established.

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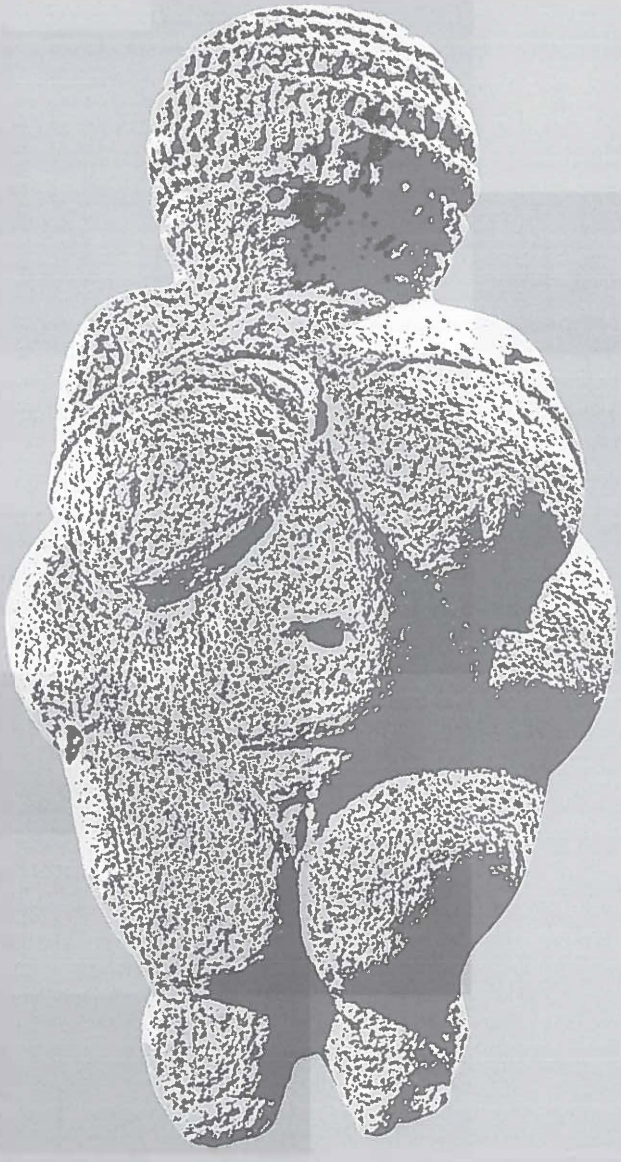

Appendix

After all those fat years: renal consequences of obesity (letter)

Chapter 7

Renate J. Bosma, Paul E. de Jong, Gerjan Navis

Nephrol Dial Transplant. 2004 Jul;19(7):1934

Sir,

With interest we read the editorial by Dr Wolf on obesity as a renal risk factor (1). We fully support the authors' view that overweight and insulin resistance, as mediators of renal risk, deserve attention not only in morbidly obese patients with overt insulin resistance, but also in renal patients with less severe obesity.

Recent data from our group suggest that their impact may be even larger, and also be relevant to subjects without overt obesity. First, we found that the relationship between body mass index (BMI) and renal hemodynamics is already apparent in subjects without overt obesity. In 102 healthy subjects with a mean BMI of 24.8 (range 16.1 to 29.7) kg/m² a higher BMI was significantly associated with a higher filtration fraction, without a threshold value. Thus, the balance between afferent and efferent glomerular arteriolar tone is already unfavourably altered at values of BMI below the overtly obese range (2).

Moreover, epidemiological data from the general population suggest that the effect of insulin resistance may also extend beyond overt obesity. In the PREVEND cohort (7676 subjects), a higher waist-hip ratio, as an indicator of insulin resistance, was associated with impaired renal function – not only in obese but also in lean subjects – defined as a BMI<25 kg/m² (3), suggesting that insulin resistance can affect renal function in the absence of obesity. This association was independent from other risk factors, such as hypertension and micro-albuminuria.

These data suggest that the mechanisms present in obese, insulin-resistant renal patients can also be encountered in subjects without overt obesity according to current definitions, and may adversely modify the course of renal function loss. As noted by Dr Wolf, it would be premature to make general recommendations. In particular, the relationship between BMI, nutritional status and overall risk profile in renal patients may not be similar to that in non-renal populations. Nevertheless, the data so far indicate that mechanisms present in overtly obese and/or insulin resistant subjects may be relevant in much larger populations than assumed so far – and definitely deserve further exploration as to their relevance in renal patients.

Renate J. Bosma
Paul E. de Jong
Gerjan Navis

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Samenvatting

Chapter 8

Het vóórkomen van overgewicht (body mass index (BMI) tussen 25 en 30 kg/m²) en obesitas (body mass index groter dan 30 kg/m²; ziekelijke vetzucht) neemt sterk toe en dreigt – door de ermee samenhangende ziekten – het grootste gezondheidsprobleem van de 21e eeuw te worden. Obesitas gaat samen met een verhoogde kans op hart- en vaatziekten. Verscheidene oorzaken dragen daartoe bij. Om te beginnen leidt obesitas vaak tot suikerziekte of het voorstadium daarvan, de zogenaamde insulineresistentie. Verder leidt obesitas vaak tot hoge bloeddruk en een verhoogd vetgehalte in het bloed. In de Verenigde Staten (VS) heeft momenteel bijna 65% van de inwoners overgewicht, terwijl er bij ruim 30% sprake is van obesitas. De situatie in Nederland is weliswaar minder ernstig, maar toch is bij zo'n 40% van de bevolking sprake van overgewicht en bij 10% van obesitas. Hoewel behandelingsmogelijkheden voor hart-en vaatziekten en voor suikerziekte aanzienlijk verbeterd zijn, is dit toch een zorgelijke ontwikkeling.

Ook voor het ontwikkelen van nierschade is obesitas een risicofactor. Het is al lange tijd bekend dat ernstige vetzucht de oorzaak kan zijn van een ziektebeeld met progressieve nierschade en eiwitverlies in de urine. Bij patiënten met een nierziekte door een andere oorzaak, en bij niertransplantatiepatiënten, kan obesitas het verlies van nierfunctie versnellen. Op dit moment is de situatie wereldwijd dusdanig dat het aantal mensen met obesitas en overgewicht blijft toenemen en er moet worden gevreesd dat overgewicht en obesitas in de nabije toekomst zullen uitgroeien tot de belangrijkste risicofactoren voor nierschade. Bij het ontstaan van die nierschade spelen de hoge bloeddruk, suikerziekte en insulineresistentie die het gevolg zijn van de obesitas waarschijnlijk een belangrijke rol. Veranderingen in de bloeddoorstroming van de nier, de renale hemodynamiek, zijn betrokken bij de schadelijke effecten van hoge bloeddruk en suikerziekte op de nier. Ook obesitas heeft waarschijnlijk ongunstige effecten op de renale hemodynamiek, niet alleen door het samengaan met hoge bloeddruk of suikerziekte, maar ook los daarvan. Beter begrip van de afwijkingen in de renale hemodynamiek en het schadelijke effect van obesitas en overgewicht op de nier is van klinisch belang, omdat de afwijkingen in de renale hemodynamiek in principe met geneesmiddelen corrigeerbaar zijn.

Dit proefschrift onderzoekt daarom de relatie tussen overgewicht en obesitas, renale hemodynamiek en nierschade bij de mens. In dierexperimentele studies is al geruime tijd geleden aangetoond dat afwijkingen in de renale hemodynamiek de nier kunnen beschadigen. Bij de mens bestaan hierover echter slechts indirecte aanwijzingen,

vooral omdat er vrijwel geen studies bestaan waarin meting van de renale hemodynamiek werd gecombineerd met langdurige follow-up van de patiënten. Wel zijn in kleine series patiënten, met veelal zeer ernstige obesitas – met doorgaans ook hoge bloeddruk en/ of suikerziekte – afwijkingen in de renale hemodynamiek gevonden die op grond van dierexperimentele studies als ongunstig worden beschouwd. Over de renale hemodynamiek bij minder extreme vormen van obesitas is echter nauwelijks iets bekend, hoewel dit een veel groter aantal mensen betreft.

Het Universitair Medisch Centrum in Groningen heeft al ruim 30 jaar ervaring in het meten van renale hemodynamiek met behulp van de merk-stoffen iothalamaat en hippuran, voor de meting van respectievelijk de glomerulaire filtratiesnelheid (GFR; de belangrijkste maat voor nierfunctie) en effectieve renale plasmaflow (ERPF, een maat voor de bloeddoorstroming van de nier). Uit de verhouding van die twee, uitgedrukt als filtratiefractie (FF), kan een indruk worden verkregen over de bloeddruk in de filtrerende haarvaatjes in de nier. Een te hoge druk in de haarvaatjes leidt weliswaar op korte termijn tot een stijging in nierfunctie, maar kan op de langere termijn de nier beschadigen. Deze meting, die beschouwd wordt als de gouden standaard voor nierfunctiemeting, wordt verricht bij specifieke patiëntengroepen, zoals patiënten die een niertransplantatie hebben ondergaan, maar ook bij mensen die worden gekeurd alvorens een nier af te staan, en bij gezonde vrijwilligers in het kader van wetenschappelijk onderzoek. De beschikbaarheid van een grote hoeveelheid metingen en patiëntengegevens biedt een uitstekende mogelijkheid de relatie tussen overgewicht, obesitas, renale hemodynamiek en nierschade in verschillende populaties in detail te bestuderen.

In de klinische praktijk, of voor epidemiologische screening, beschikt men meestal niet over de door ons gebruikte nierfunctiemeting. Vaak wordt daarom gebruik gemaakt van de zogenaamde nierfunctie-formules, waarvoor alleen het kreatininegehalte in het bloed nodig is om de nierfunctie te berekenen. Dit is namelijk gemakkelijk en goedkoop. Deze formules hebben echter aanzienlijke tekortkomingen. Eén daarvan is, dat de uitkomst ervan gestoord wordt door verschillen in lichaamsbouw, zoals bij overgewicht en obesitas. Daardoor kan een systematische fout in de nierfunctieschatting optreden die het onderzoeken van de relatie tussen overgewicht/obesitas en nierfunctie stoort. In **hoofdstuk 2** onderzochten we of een dergelijke systematische fout optreedt bij patiënten die een niertransplantatie hadden ondergaan. Na een niertransplantatie

worden patiënten namelijk meestal zwaarder door het wegvallen van de dieet-beperkingen, samen met de (eetlust-versterkende) medicijnen (prednisolon). We vonden inderdaad een dergelijke systematische fout bij alle onderzochte formules. De meest gebruikte formule, de MDRD formule, onderschatte de GFR méér naarmate de BMI toenam. De eveneens veel gebruikte Cockcroft-Gault formule daarentegen gaf juist een forse overschatting van de GFR bij toenemende BMI. Bij gebruik voor het vervolgen van de nierfunctie in de individuele patiënt, was de systematische afwijking van de formules minder storend, maar desondanks is uit onze gegevens duidelijk dat de beschikbare formules verre van ideaal zijn. Voor analyse van de rol van overgewicht en obesitas op de nierfunctie zijn ze dan ook niet geschikt, en onze verdere studies wordt alleen gebruik gemaakt van de gouden standaard-methode.

Er zijn veel (dier)experimentele studies waarin de invloed van obesitas op de renale hemodynamiek wordt onderzocht. Studies bij de mens zijn echter zeldzamer, en betreffen vrijwel uitsluitend mensen met ernstige vetzucht. In **hoofdstuk 3** onderzochten we daarom de relatie tussen BMI en renale hemodynamiek bij gezonde personen met een BMI<30 kg/m². In deze populatie ging een hogere BMI gepaard met een hogere FF. Overgewicht was dus geassocieerd met een ongunstige verandering in renale hemodynamiek, zonder dat er sprake was van (ernstige) obesitas, en zonder een duidelijke ondergrens van BMI voor wat betreft de invloed op de nier. Dit sluit aan bij recente epidemiologische gegevens die laten zien dat het lange termijn risico op nierschade niet beperkt is tot personen met manifeste obesitas, maar ook al aantoonbaar is bij overgewicht. Onze resultaten laten ook zien dat de invloed van BMI op de renale hemodynamiek in principe niet afhankelijk is van bijkomende aandoeningen zoals hoge bloeddruk en suikerziekte. Wel was een relatie met de leeftijd aanwezig. In personen met een hogere BMI verliep namelijk de daling van GFR (zoals die altijd wordt gezien met toenemen van de leeftijd) meer uitgesproken. Omdat het hier een dwars-doorsnede onderzoek (dat wil zeggen, op één moment in de tijd gemeten) betreft, moet de relatie met leeftijd echter voorzichtig worden geïnterpreteerd. Ons onderzoek rechtvaardigt de hypothese dat veranderingen in renale hemodynamiek betrokken zijn bij het ontstaan van nierschade ten gevolge van overgewicht, maar om deze hypothese daadwerkelijk te bewijzen, zou lange termijn vervolg onderzoek nodig zijn. Het zou daarbij overigens interessant zijn om het effect van bijkomende aandoeningen zoals hoge bloeddruk en suikerziekte te analyseren.

We bespraken al, dat obesitas bij patiënten met een nierziekte een ongunstig effect op het beloop van de nierschade kan hebben. In hoeverre een hogere BMI ook bij nierziekte een ongunstig effect heeft op de renale hemodynamiek is tot dusverre onbekend. In **hoofdstuk 4** onderzochten we daarom de relatie tussen overgewicht en obesitas, de renale hemodynamiek, en de uiteindelijke prognose bij niertransplantatie patiënten. De eerste vraag was of BMI van invloed is op de renale hemodynamiek bij deze patiënten, omdat de resultaten van studies bij "eigen" nieren niet direkt kunnen worden vertaald naar de getransplanteerde nier. Deze is namelijk in meerdere opzichten wezenlijk anders. Ten eerste moet deze ene nier "al het werk" alleen doen, hetgeen waarschijnlijk effect heeft op de renale hemodynamiek. Ten tweede is de nier ten tijde van de operatie enige tijd buiten een menselijk lichaam geweest, waardoor schade kan zijn ontstaan. Ten derde worden na transplantatie afweeronderdrukkende medicijnen voorgeschreven die de haarvaatjes in de nier kunnen beschadigen. Daarnaast is het waarschijnlijk relevant dat de getransplanteerde nier geen eigen zenuwvoorziening meer heeft. In vergelijking met een "eigen nier" reageert deze dus anders – of niet – op signalen die door het lichaam worden afgegeven. De getransplanteerde nier is ook nog om een andere reden interessant: de erfelijke eigenschappen en achtergronden van de nier en de ontvanger zijn immers verschillend. Het is dus om verschillende redenen interessant na te gaan of een hogere BMI van de ontvanger van de nier gekoppeld is aan een specifiek hemodynamisch profiel in de getransplanteerde nier. Nog interessanter, en van klinisch belang, zou het zijn te weten of een verband tussen een hogere BMI en slechtere prognose van de getransplanteerde nier toe te schrijven valt aan veranderde renale hemodynamiek. Om deze twee vragen te beantwoorden onderzochten we eerst in een dwarsdoorsnede onderzoek het verband tussen BMI en renale hemodynamiek in een grote groep niertransplantatiepatiënten, 1 jaar na transplantatie. Net als bij de gezonde personen beschreven in het vorige hoofdstuk, vonden we ook na niertransplantatie een hyperfiltratie profiel, met een hogere FF in patiënten met een hogere BMI. Met andere woorden: de donor-nier "weet" of hij zich in een slanker dan wel dikker lichaam bevindt. Het verband tussen BMI en renale hemodynamiek stond los van het feit of de patiënten wel of geen suikerziekte hadden. Ook 5 jaar na transplantatie was nog steeds een verband aanwezig tussen BMI en renale hemodynamiek. Een lagere GFR of een hogere FF, bleken, los van elkaar en van andere risicofactoren, voorspellend voor de kans op transplantaatfalen, al dan niet door overlijden van de patiënt. Verder waren een lagere GFR en een hogere BMI eveneens voorspellend voor het optreden van transplantaatfalen nadat de overleden patiënten buiten beschouwing

waren gelaten. Deze gegevens ondersteunen de hypothese dat de veranderingen in renale hemodynamiek die worden gezien bij overgewicht een oorzakelijke rol spelen bij chronisch progressieve nierschade. Voor zover ons bekend is dit de eerste studie bij de mens die de ongunstige prognostische betekenis aantoont van een hogere FF voor de nierfunctie op de lange termijn.

Zoals hierboven beschreven kan hyperfiltratie bij de mens worden opgespoord door de nierfunctie te meten met speciale merkstoffen. De interpretatie daarvan is echter lastig als de totale GFR normaal of verlaagd is. Er kan dan op niveau van de individuele nierfiltertjes wel degelijk sprake zijn van hyperfiltratie, bijvoorbeeld als functionerend nierweefsel verloren is gegaan. Via een omweg, het meten van de reserve capaciteit van de nier, kan desondanks een indruk worden gekregen over de aanwezigheid van eventuele hyperfiltratie. De nier heeft normaal gesproken een grote reserve, zoals blijkt uit de stijging van GFR en ERPF in de resterende nier na nierdonatie, of tijdens zwangerschap. Een afname in reservecapaciteit wordt wel beschouwd als een teken van hyperfiltratie. Een maat voor de reservecapaciteit kan worden gekregen door toediening van vaatverwijders zoals dopamine en aminozuren, die leiden tot vaatverwijding vóór respectievelijk na het nierfiltertje. De combinatie van beide geeft maximale vaatverwijding met daardoor toename van GFR en ERPF: deze stijging wordt beschouwd als maat voor de reservecapaciteit. Als functionerend nierweefsel verloren gaat, bijvoorbeeld wanneer één nier verwijderd moet worden in verband met ziekte, of ten behoeve van transplantatie, spreekt de resterende nier (of het resterende nierweefsel) de reservecapaciteit aan, teneinde een zo normaal mogelijke totale nierfunctie te handhaven, en dit uit zich als een minder sterke respons op de bovengenoemde vaatverwijders. In **hoofdstuk 5** onderzochten we de relatie tussen BMI, renale hemodynamiek en renale reservecapaciteit voor en na het afstaan van een nier (donatie). We testten hiermee of het renale hemodynamische patroon bij overgewicht een afspiegeling zou kunnen zijn van hyperfiltratie. Zo ja, dan zou bij een hogere BMI sprake moeten zijn van een geringere respons op de vaatverwijders. Zoals verwacht was na donatie de gemiddelde reservecapaciteit kleiner geworden. Voor donatie was er géén relatie tussen BMI en renale reservecapaciteit, maar na donatie was de renale reservecapaciteit beduidend lager in donoren met een hogere BMI dan in donoren met lagere BMI. Dit suggereert dat het renaal hemodynamisch patroon bij een hoge BMI inderdaad berust op het aanspreken van de filtratie-reserve. Ook de relatie tussen leeftijd en reservecapaciteit vertoonde een dergelijk patroon. Voor donatie was er geen

relatie tussen leeftijd en reservecapaciteit, maar na donatie was de reservecapaciteit lager in oudere donoren. Dit suggereert dat ook bij het ouder worden de reservecapaciteit van de nieren wordt aangesproken.

Het proefschrift wordt afgesloten met **hoofdstuk 6**, waarin een overzicht wordt gegeven van de literatuur over de relatie tussen BMI en renale hemodynamiek, en de pathofysiologische consequenties daarvan. Hierin concluderen we dat obesitas en overgewicht gepaard gaan met veranderingen in renale hemodynamiek, gekenmerkt door een hyperfiltratieprofiel dat zich doorgaans uit in een verhoogde FF. Deze veranderingen kunnen niet alleen schade aan de nierfiltertjes toebrengen, ze zorgen er ook voor dat de nieren onvoldoende zout uit het lichaam verwijderen, hetgeen tot verhoogde bloeddruk aanleiding kan geven. Dit is niet alleen schadelijk voor de nier, maar ook voor hart en bloedvaten. Onze studie in transplantatiepatiënten heeft laten zien dat een dergelijk renaal hemodynamisch profiel inderdaad prognostisch ongunstig is. Op grond van deze resultaten is het logisch te veronderstellen dat de effecten van overgewicht op de renale hemodynamiek tevens bijdragen aan de kwetsbaarheid van de nier voor de gevolgen van suikerziekte en/of hoge bloeddruk.

Zoals eerder vermeld baart de toenemende prevalentie van overgewicht en obesitas veel zorgen. In studies uit het verleden bleek een hoge BMI samen te gaan met een toegenomen sterfte, vooral in de jongere leeftijdscategorieën. In recenter onderzoek echter is in de categorie personen met een BMI tussen de 25 en 30 kg/m² juist sprake van een lagere sterfte dan in de lagere BMI categorieën, en zelfs in de categorie 30-35 kg/m² lijkt er geen oversterfte te zijn. Betekent dit dat het wel wat meevalt met de risico's van overgewicht? Het is hierbij belangrijk in ogenschouw te nemen dat sinds de jaren '70 van de vorige eeuw een afname van de totale sterfte aan hart- en vaatziekten wordt waargenomen. Dit komt door een gecombineerd effect van betere behandeling van het hartinfarct, verhoogde bloeddruk, verhoogd cholesterolgehalte en suikerziekte met medicijnen en leefregels. Omdat deze aandoeningen vooral voorkomen bij overgewicht en obesitas, treft de daling van de totale sterfte vooral deze groep personen - dit wordt met name gezien in de oudere leeftijdscategorie. De daling in sterfte betekent echter nog niet, dat dikkere mensen gezonder zijn dan slanke, het is eerder zo, dat ze aan de aan de overgewicht-gerelateerde aandoeningen niet meer overlijden. Daar komt nog bij dat overgewicht en obesitas juist weer beschermen tegen andere, potentieel levensbedreigende, aandoeningen zoals heupfracturen, aandoeningen aan de luchtwegen en

infecties. Met andere woorden, ouderen met een verhoogde BMI leven relatief langer dan hun slankere leeftijdsgenoten. Het is aannemelijk dat dit meespeelt in het toenemende belang van overgewicht als oorzaak voor nierschade: door de verbeterde overleving bij hart-en vaat-ziekten is er immers "meer tijd" om chronische nierschade te ontwikkelen, een zorgelijk scenario waar derhalve ernstig rekening mee moet worden gehouden, zoals ook al werd aangestipt aan het begin van deze samenvatting.

Het is echter wel bemoedigend te realiseren dat het ongunstige renale hemodynamische profiel bij overgewicht en obesitas gunstig kan worden beïnvloed door gewichtsverlies en met medicijnen die ingrijpen in het renine-angiotensine systeem, zoals angiotensine converting enzyme (ACE)-remmers en angiotensine receptor antagonisten. Een recente studie van onze groep toonde bovendien aan dat ook een zoutbeperkt dieet de effecten van overgewicht op de renale hemodynamiek corrigeert. Logischerwijs is gewichtsreductie de belangrijkste maatregel voor risicoreductie. Duurzame gewichtsreductie is over het algemeen echter moeizaam, al lijkt een relatief nieuw middel, de cannabis receptor antagonist Rimonabant®, mogelijk enig perspectief te bieden in risico groepen. Onze gegevens suggereren dat interventie in de renale hemodynamiek, hetzij door medicatie, hetzij door zoutbeperking, de nier zou kunnen beschermen tegen de schadelijke gevolgen van overgewicht. Of dat daadwerkelijk zo is, moet echter in lange termijn studies worden uitgezocht.

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